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## COMPREHENSIVE REVIEW OF UROLLO CY

directed by Aria F. Olumi, MD

BETH ISRAEL DEACONESS MEDICAL CENTER

#### Comprehensive Review of Urology Provided by: Oakstone Publishing, LLC

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#### **TARGET AUDIENCE:**

The activity was designed to provide urologists, urology fellows and residents, surgery residents interested in urology, other licensed individual practitioners or ancillary staff interested in urology, or who participate in the delivery of urologic care with current, relevant, and condensed information needed to pass certification and recertification exams.

#### **ESTIMATED TIME TO COMPLETE:**

It is estimated that it should take the average learner 56 hours to complete the activity.

#### **ACCREDITATION:**

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Contact Hours: 56

**SPECIAL PREREQUISITES FOR PARTICIPANTS:** There are no prerequisites for participants.

**METHOD OF PARTICIPATION:** Review Video/Audio program, score 70% or greater on the required posttest to assess the knowledge gained from reviewing the program and complete the comprehensive activity evaluation.

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#### **LEARNING OBJECTIVES:**

At the conclusion of this activity, the participant will be able to:

- Discuss the discrete urologic infections and inflammatory disorders and how they are best managed.
- Describe the best surgical approaches for urologic trauma.
- Identify the ideal treatment approaches for patients with kidney cancer.
- Differentiate between non-muscle invasive bladder cancer and muscle invasive bladder cancer.
- Summarize the most efficacious therapies for bladder cancer.
- Differentiate between medical approaches and surgical approaches for prostate cancer.
- Describe active surveillance in prostate cancer.
- Assess the importance of adolescent and transitional urology.
- List common and uncommon urologic conditions in children.
- Define male and female sexual dysfunction.
- Explain evaluation and medical and behavioral management of urinary incontinence in women.
- Distinguish among the benefits of medical and surgical management of lithiasis.

#### FACULTY AFFILIATIONS DISCLOSURE:

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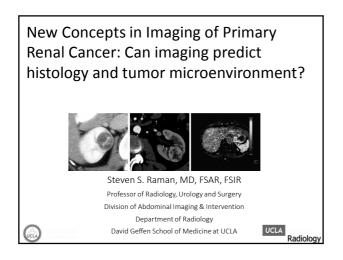
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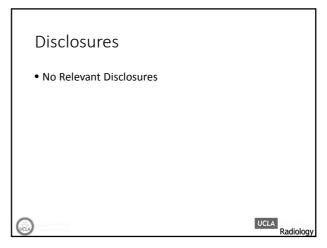
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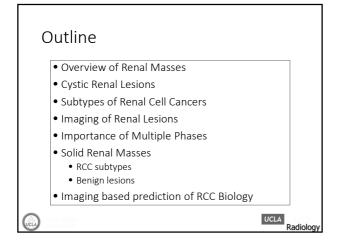
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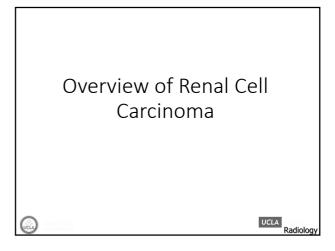
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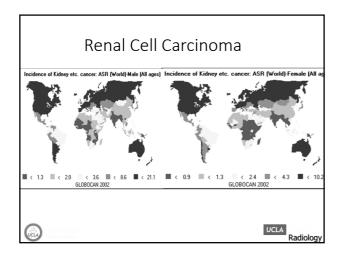
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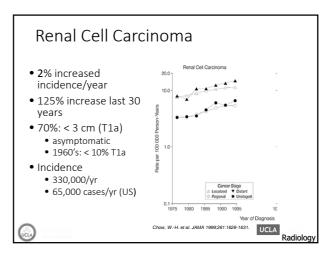




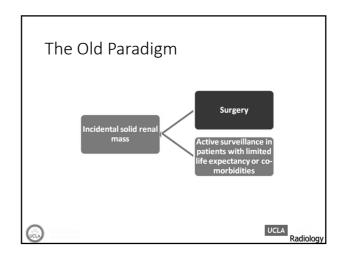


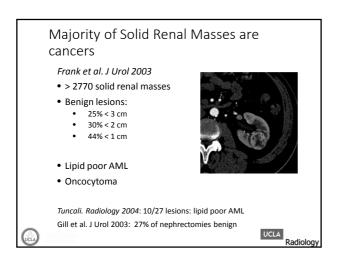


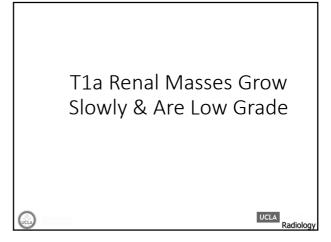


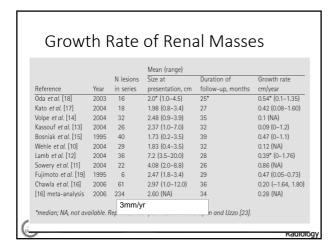


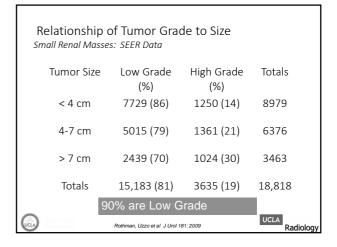
All Solid Renal Masses Need to Come out, Right ?

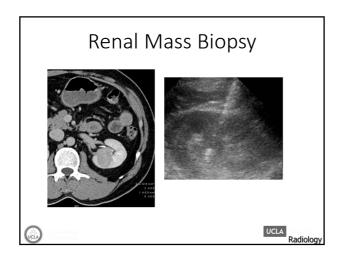


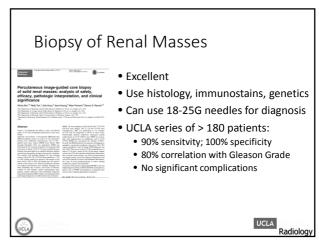


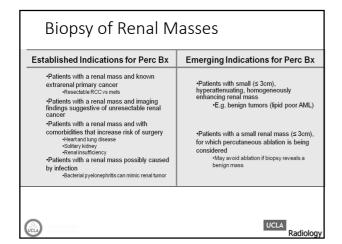


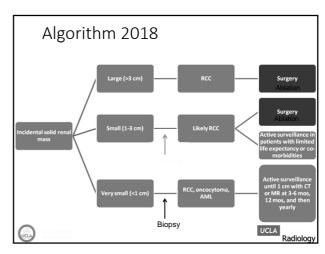




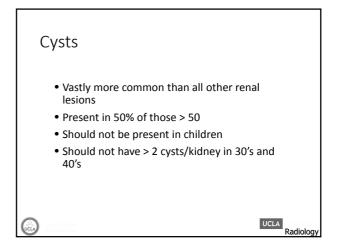








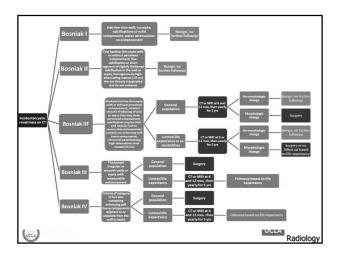
Cystic Renal Lesions

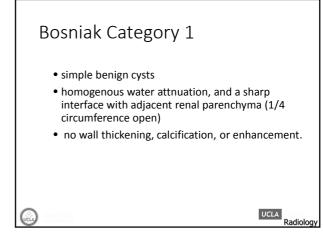


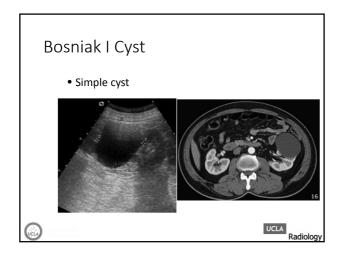
# Complex Cysts • Cysts may be complicated by hemorrhage, infection, ischemia • Resulting in: • Septations • Calcifications • Internal debris • But not mural nodules

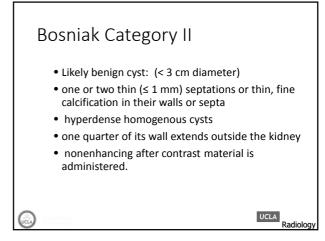
# Bosniak Classification CT or MR based stratification of cysts to assign a probability of malignancy Bosniak I and II: non surgical Bosniak III and IV: surgical due to 60 – 90% chance of malignancy

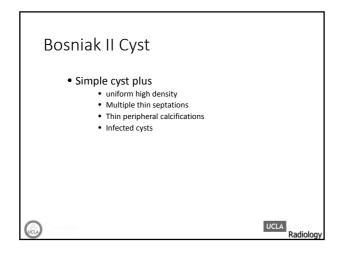
UCLA

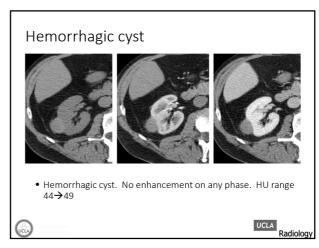


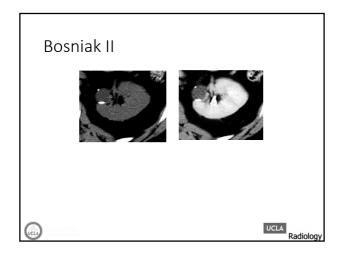


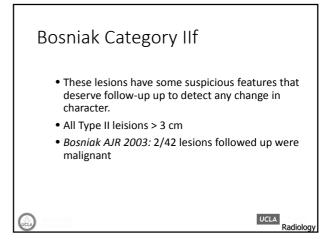


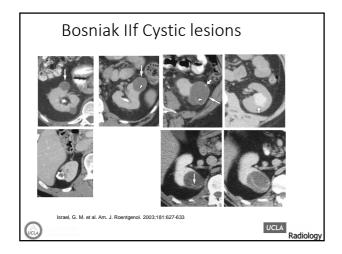


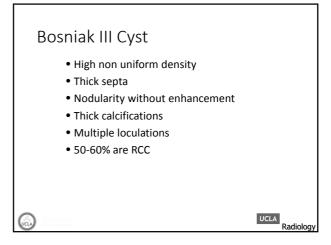


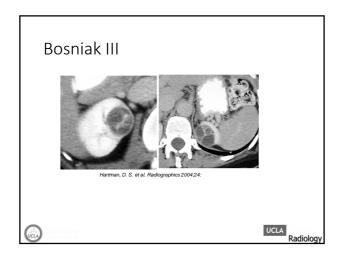


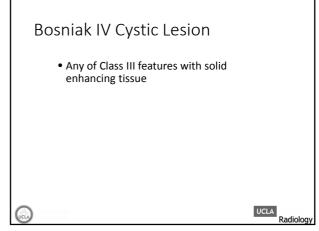


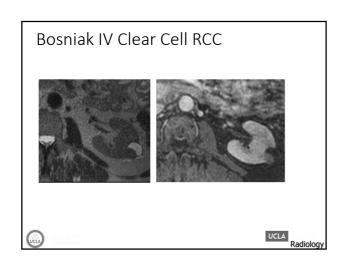




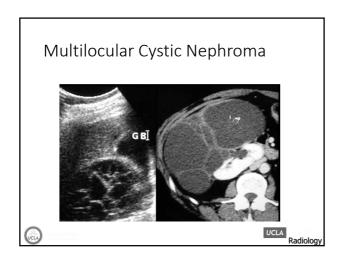


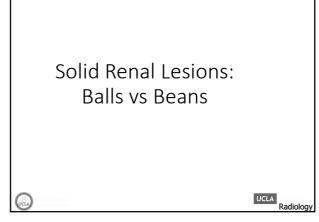


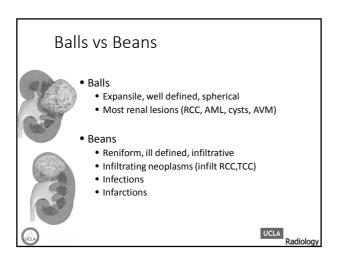


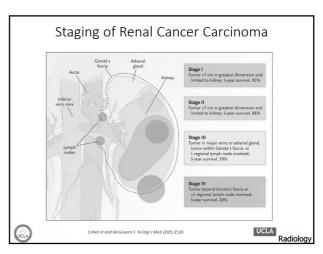


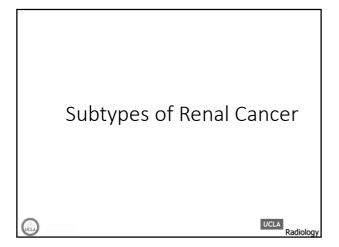




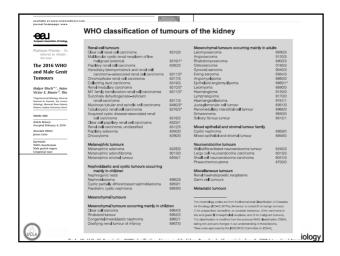


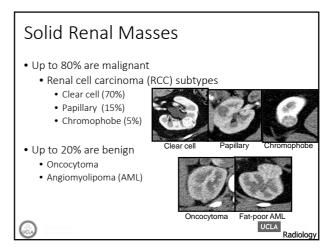


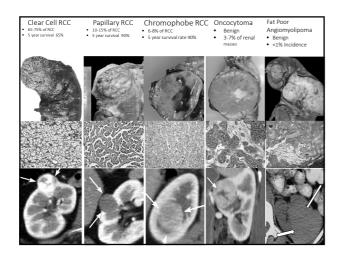


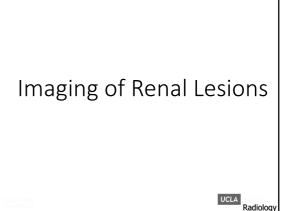












#### UCLA CT Protocol for Renal Mass Detection and Follow up

- On 16-64 detector CT
  - Unenhanced scan
  - Enhanced scan phases:
    - Inject 100-150 cc Omnipaque 350 @ 3-4 cc/sec
    - Bolus tracking (image @ 25 sec after aorta HU > 150 )
    - Corticomedullary phase scan (45 sec)
    - Nephrogenic phase scan (80-90 sec)
    - Excretory phase scan (3 min)



#### UCLA MR Protocol for Renal Mass Detection and Follow up

- Axial & Coronal SSFSE/HASTE T2
- Axial multishot FSE/TSE T2
- Axial dual echo GRE T1
- Axial 2D or 3D GRE T1 w/ fat sat
- Dynamic 2D or 3D GRE T1 w/fat sat at 30, 60, 90, 120 & 180 sec after injection of 0.1mmol Gd @ 2cc/sec
- Subtraction imaging
- Diffusion (b 0, 50, 400, 800) / ADC
- Feraheme (4mg/kg)



UCLA Radiology

#### Ultrasound

- Grayscale
- Color, Power and Spectral Doppler
- Microbubble Contrast
  - Definity 0.3 cc/injection with 10 cc saline flush
  - Lumason 2.4 cc/injection with 10cc saline flush



UCLA Radiology

#### Corticomedullary Phase



- Contrast in cortical capillaries, peritubular spaces and proximal cortical tubular lumina
- Cortex enhances brightly, medulla not yet opacified
- Intense corticomedullary differentiation (>100 HU)

UCLA

CLA

#### Uniform Nephrogram Phase



- Greatest yield for detection in this phase (84 more lesions < 3 found on NP vs CM\*)</li>
- 1.5 x detection of cystic & solid masses with NP vs CM phase\*\*
- Assessment of deenhancement for characterization
- Greatest temporal variability, however, depending on
  - Injection rate, contrast volume & cardiac output

\*Szolar et al., Radiology 1997;202:211

\*\*Cohan et al. Radiology 1995;196:445



#### **Excretory Phase**



- Identification and staging of upper tract transitional cell carcinoma
- Defines relationship of a central mass to the collecting structures
- Allows evaluation of de-enhancement\* (Washout ROI at 15 minutes differentiates between hyperdense cyst and neoplasm)

\*Macari, Bosniak. Radiology 1999;213:674



Radiology

#### **Enhancement**

- ROI should incorporate only the most attenuating portion of the lesion in all phases
- Avoid calcifications & low attenuation areas
- Minimal threshold value: 15 -20 HU
- Pseudoenhancement
  - Small cysts (<1.5 to 2 cm) "enhance" due to surrounding high attenuation (? Beam hardening, reconstruction algorithm)
  - Effect is greater with MDCT than single slice
  - Matrix detector array > adaptive array

Abdulla, et al. AJR 2002;179:1473



#### Diagnosing Renal Lesions

- Cystic or Solid
- Lesion Margin
- Macroscopic & Microscopic Fat
- Density on non-contrast CT
- Echogenicity on US
- T2 Signal
- Enhancement pattern
  - CM, Nephrographic & Excretory phase
  - CT, MR and US

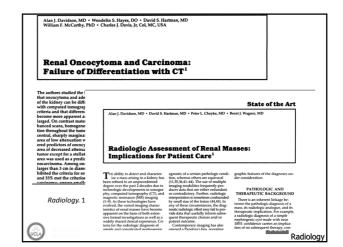


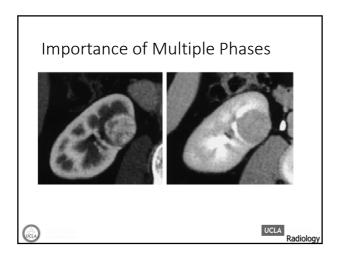
UCLA Radiology

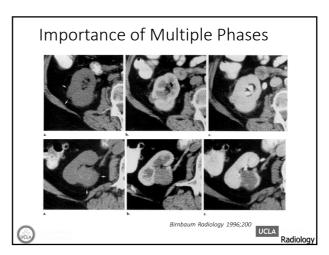
Importance of Multiple Phases

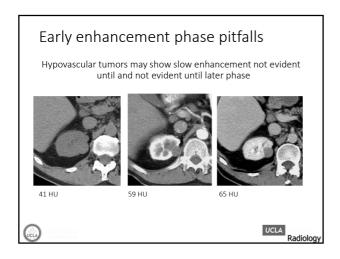


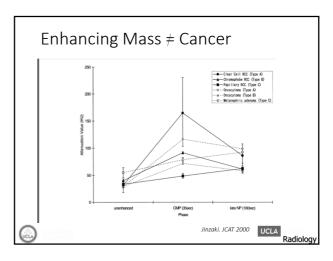
Radiology

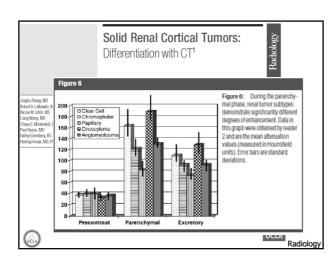


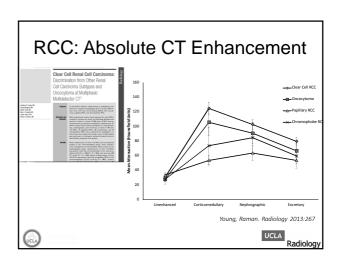


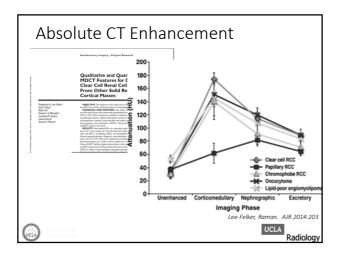


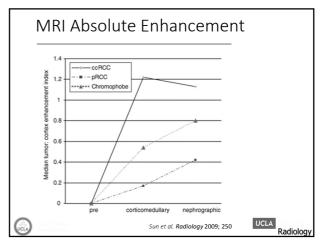


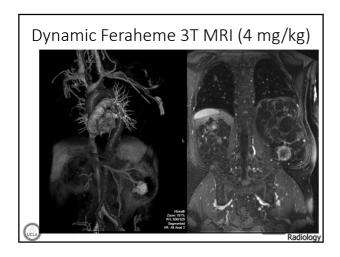


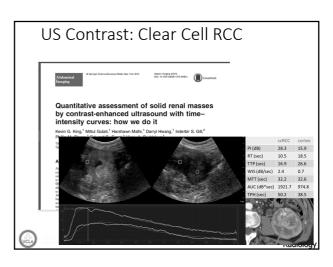


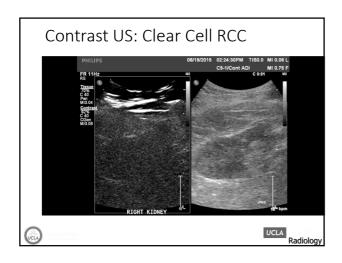


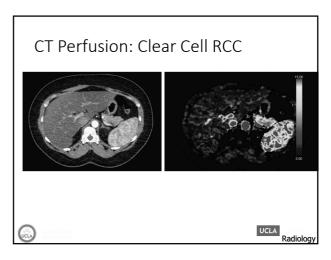


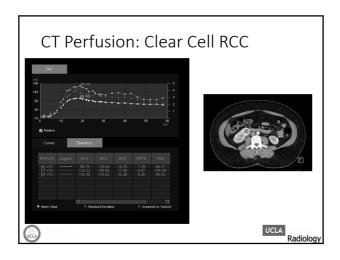


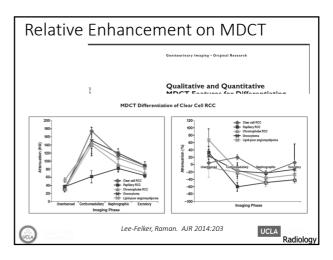


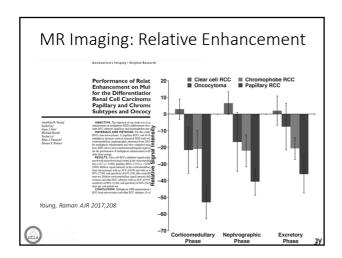


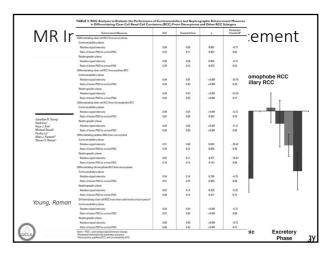


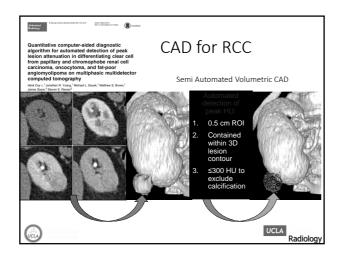


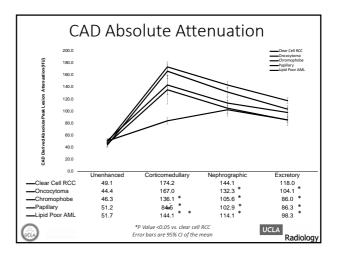


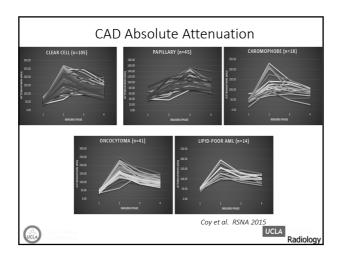


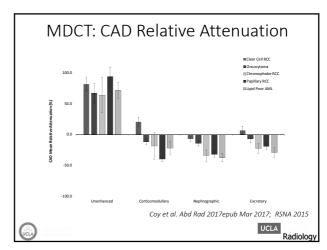


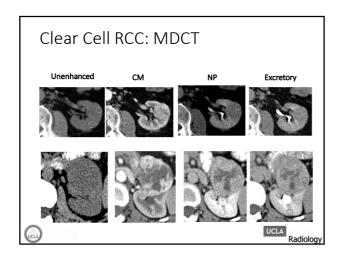


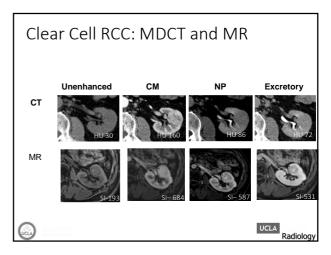


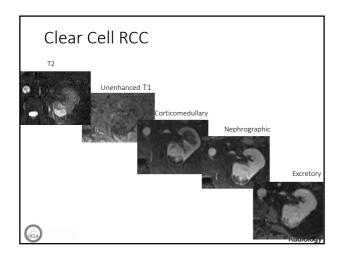


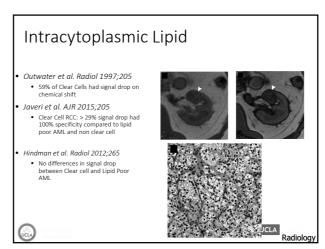


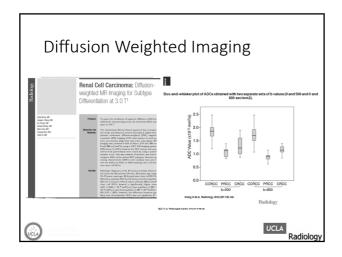


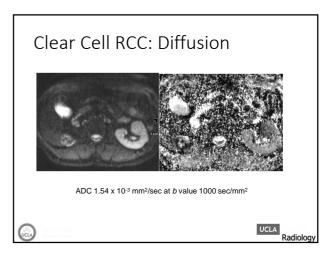


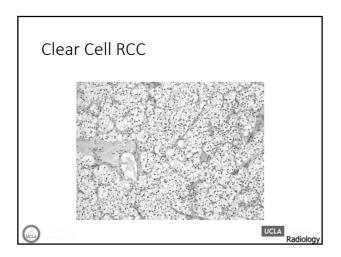


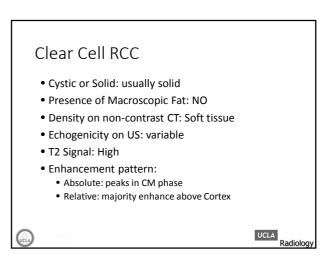


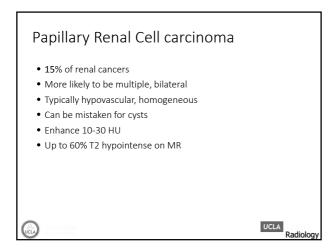


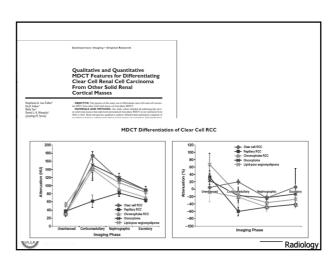


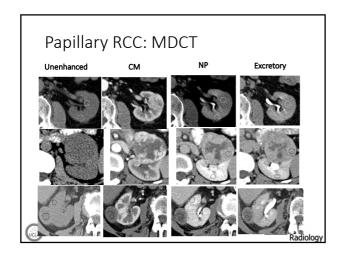


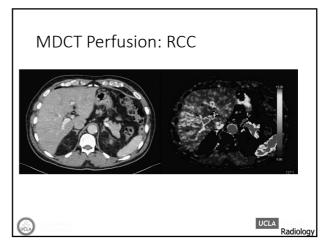


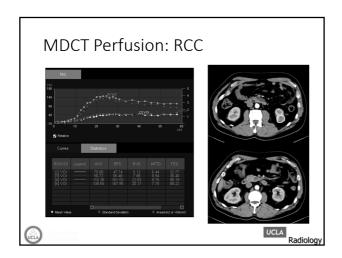


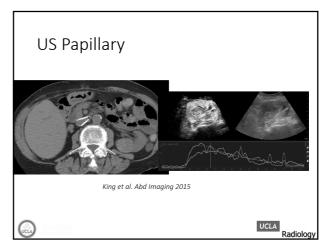


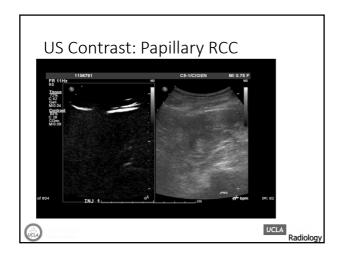


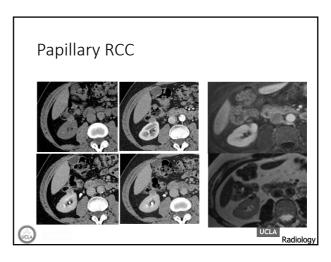


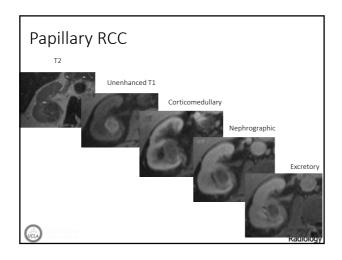


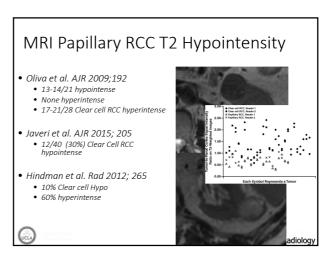


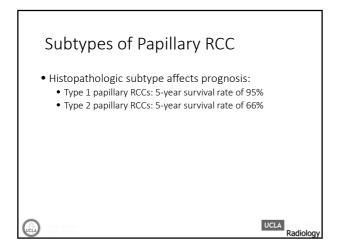


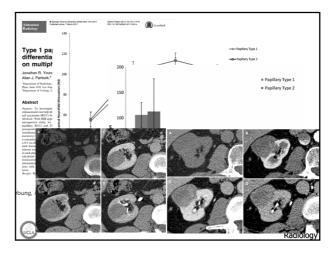


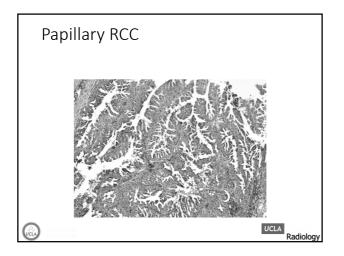


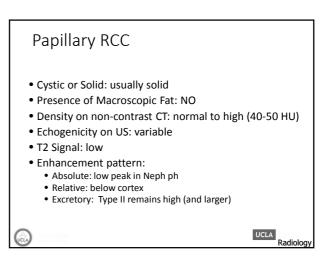




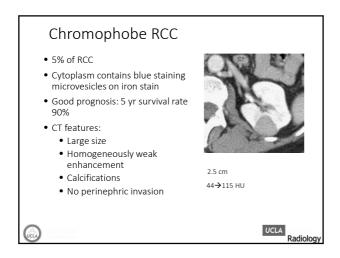


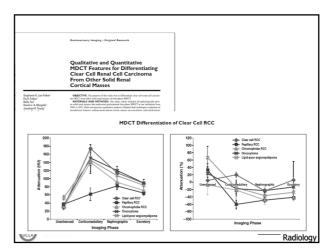


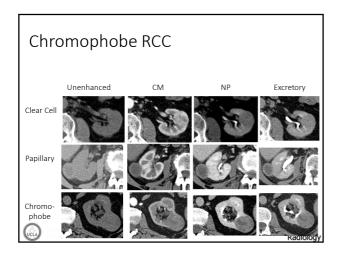


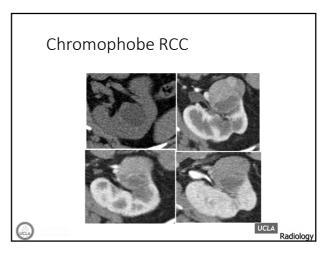


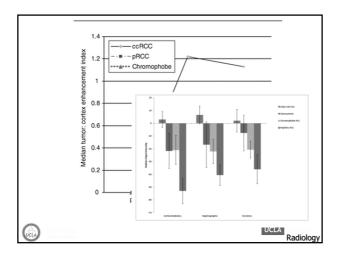
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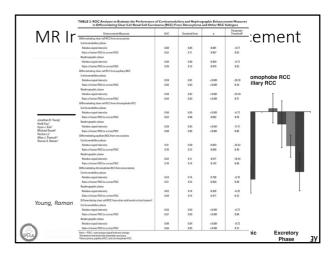


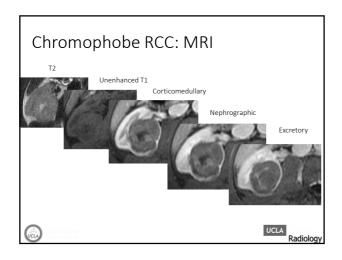


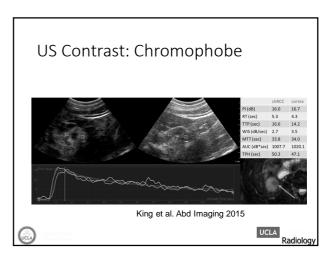


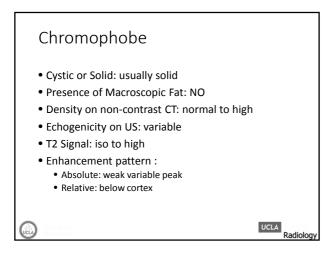


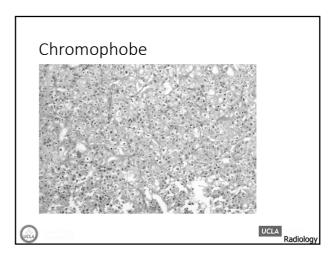


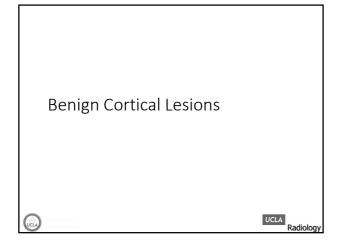


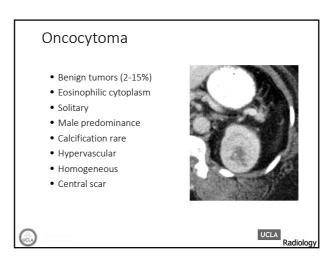


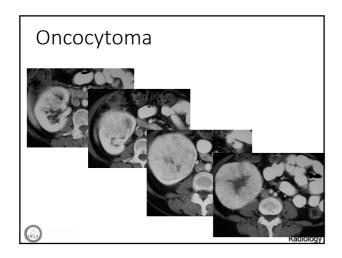


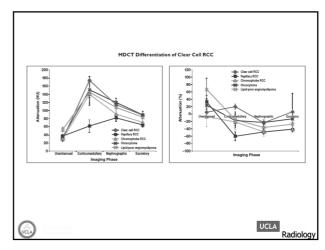


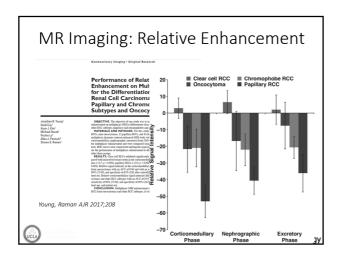


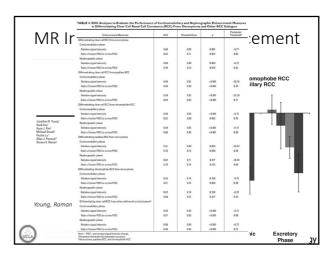


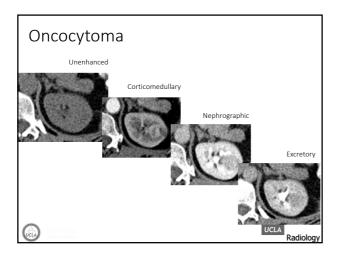


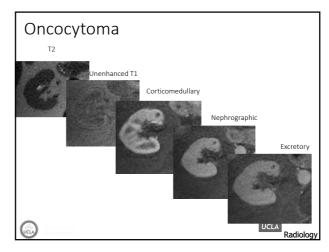


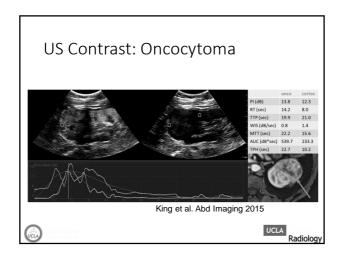


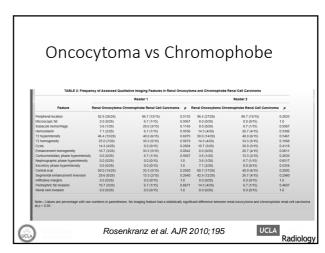


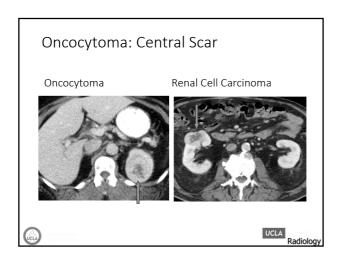


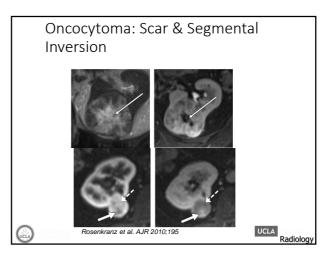


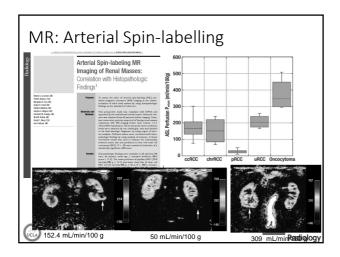




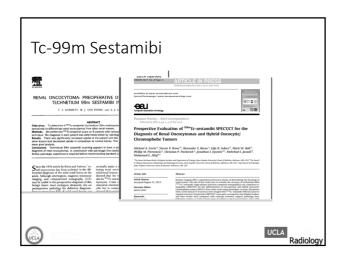


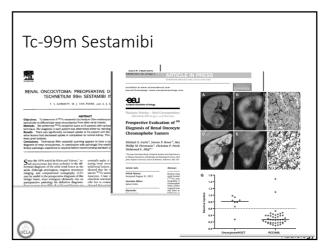


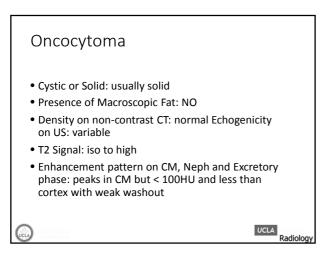


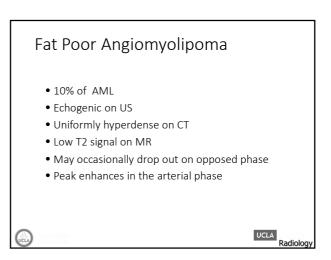


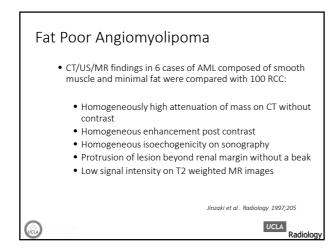


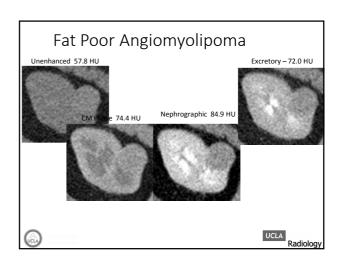




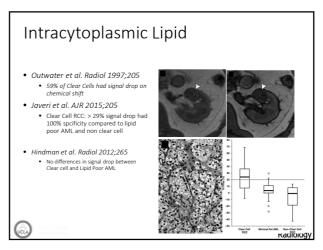


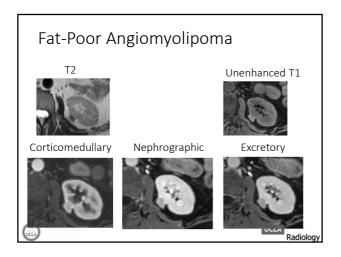


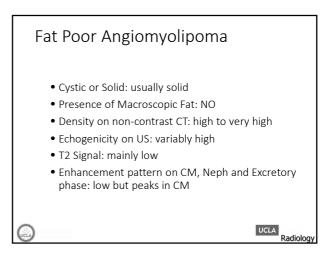


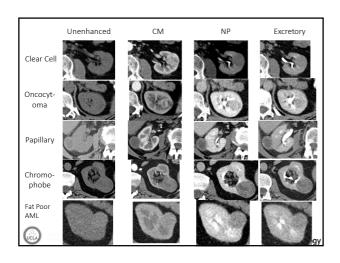


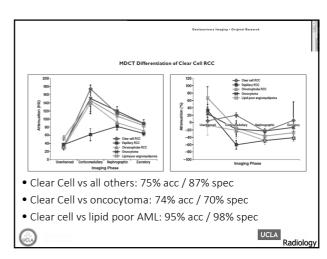




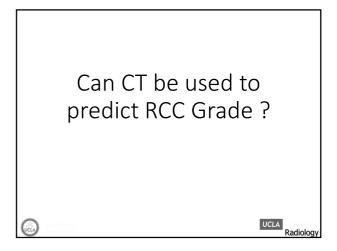


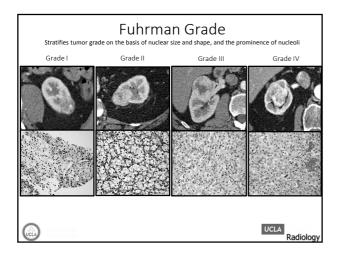


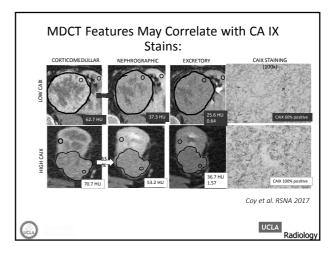




Imaging Based Prediction of RCC Biology







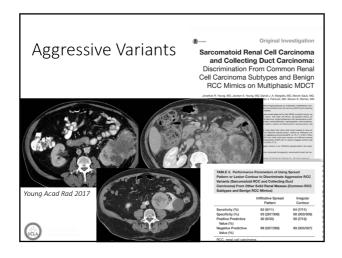
Can MDCT Imaging
Features Discriminate
Common Subtypes of RCC
from Aggressive RCC
Variants?

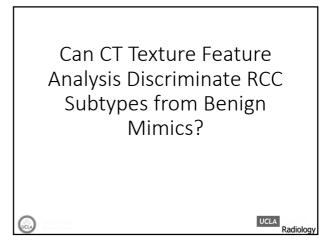
UCLA Radiology

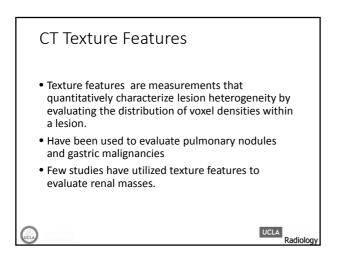
#### Aggressive RCC Variants

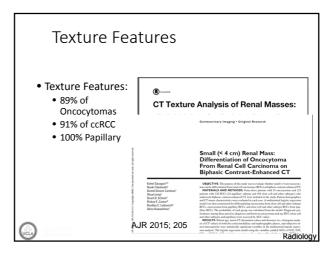
- Sarcomatoid RCC and collecting duct carcinoma should be managed differently than more common RCC subtypes, namely clear cell.
  - Clear cell RCCs are typically surgically resected
  - For sarcomatoid RCC and collecting duct carcinoma, surgical resection prior to systemic therapy may actually worsen outcomes
  - 45-84% of patients with collecting duct and sarcomatoid RCC have distant metastases at the time of diagnosis.

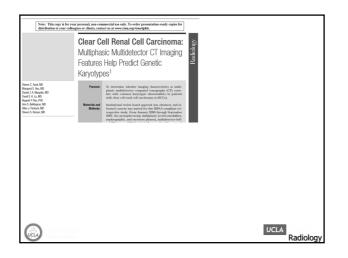
UCLA Radiology

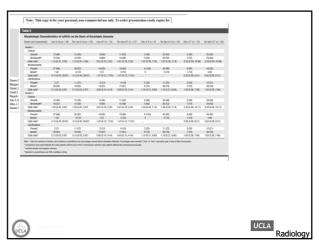


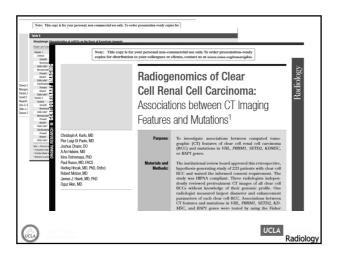


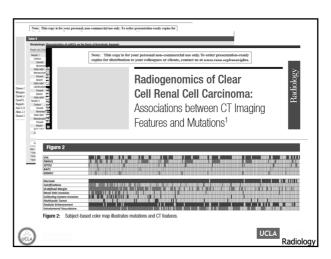


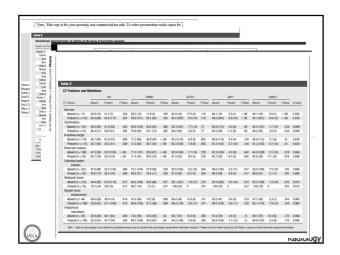


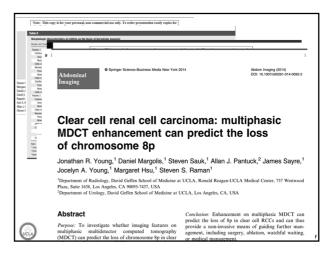


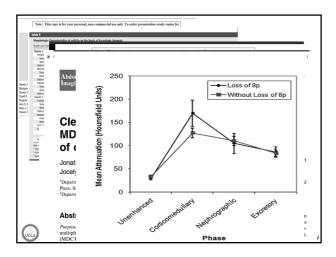


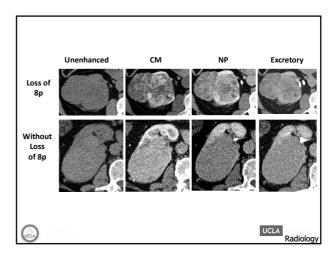


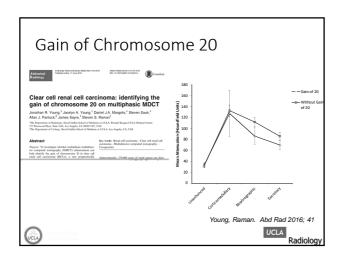


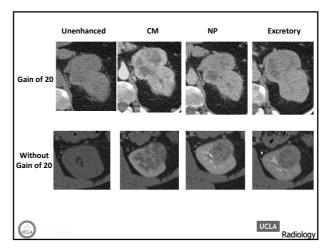


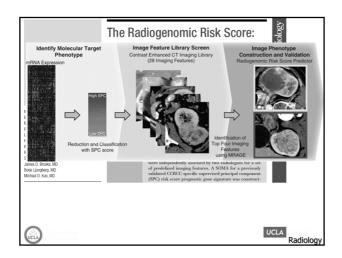


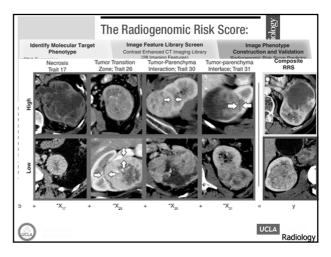


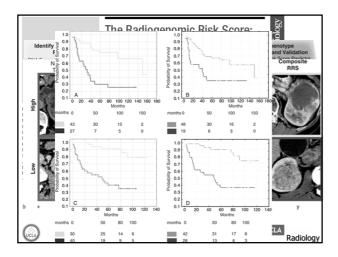














### Summary

- A significant minority of renal masses are benign
- Cystic renal lesions are indolent
- Solid renal masses grow 2-3 mm/yr
- Biopsy is very effective for discrimination
- Imaging can characterize the majority of renal masses
- Imaging can help grade clear cell RCC
- Imaging can possibly distinguish papillary type 1 from type 2
- Imaging can help predict clear cell cytogenetics
- Biopsy is safe and effective



JCLA Radiolog

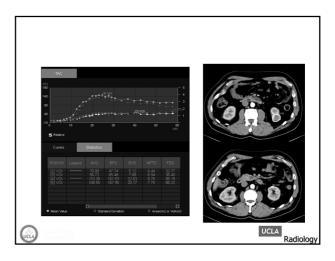
### Summary

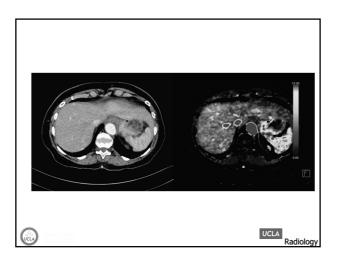
- Multiphasic CT & MR are necessary for characterization
- Imaging can characterize the majority of renal masses
- Imaging can help grade clear cell RCC
- Imaging can possibly distinguish papillary type 1 from type 2
- Imaging can help predict clear cell cytogenetics

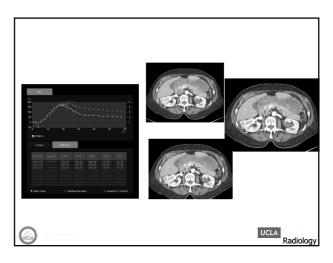


Radiology

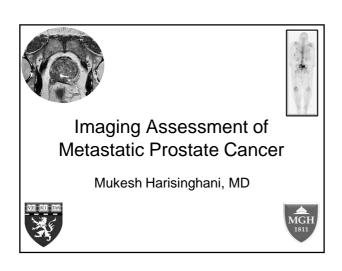








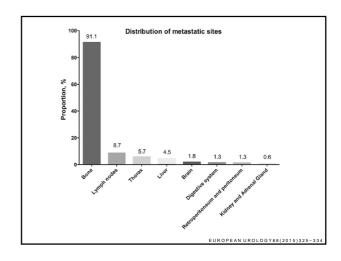
• None

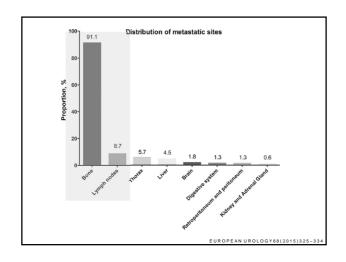


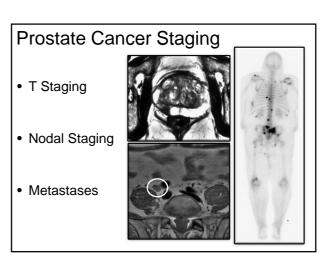
### Disclosures

### Overview

- Clinical overview of metastatic prostate cancer
- Imaging techniques
  - Benefits and Limitations











T3 non organ confined tumor → adjuvant radiotherapy after surgery or adjuvant hormone therapy after radiotherapy

### **Prostate Cancer**



T3 non organ confined tumor → adjuvant radiotherapy after surgery or adjuvant hormone therapy after radiotherapy



N1 spread to regional LN→ recommendation is androgen deprivation therapy → increasingly recognized as benefiting from radiotherapy





T3 non organ confined tumor → adjuvant radiotherapy after surgery or adjuvant hormone therapy after radiotherapy



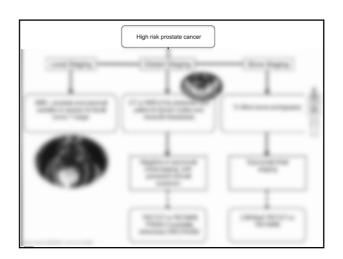
M1 distant metastases→ asymptomatic → at this time unproven to benefit from initial local therapy

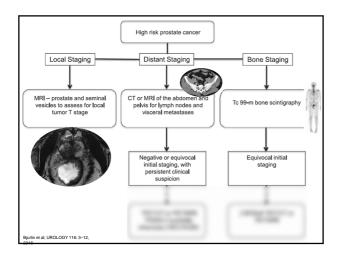
### NCCN Risk Stratification for PCa

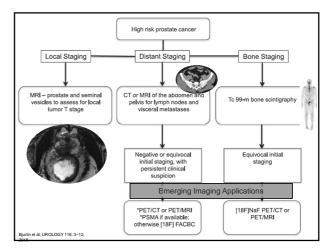
Risk Category	Clinical T Stage	Gleason Score	PSA (ng/mL)
Very low <sup>a</sup>	T1c	$\leq$ 6 (Fewer than 3 cores each with $\leq$ 50% cancer)	<10 (PSA density <0.15 ng/mL/g)
Low <sup>b</sup>	T1-T2a	≤6	<10
Intermediate <sup>b</sup>	T2b-T2c	7	10-20
High <sup>b</sup>	T3a	8–10	>20
Very high <sup>b</sup>	T3b-T4	Primary pattern 5 or >4 cores with Gleason score 8–10	_

### NCCN Risk Stratification for PCa

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Very high <sup>b</sup>	T3b-T4	Primary pattern 5 or >4 cores with Gleason score 8–10	_	







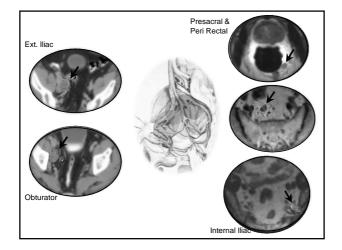
### Lymph Node Staging

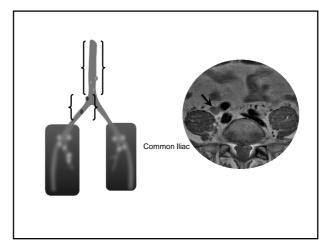
- Achilles heel → imaging
  - Size and Morphology
- PET and New MR techniques

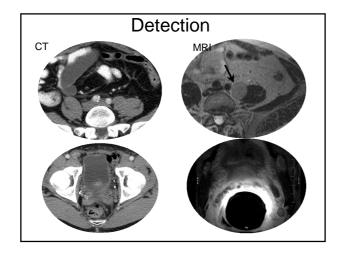
### Lymph Node Staging

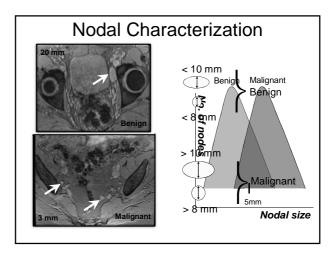
- Achilles heel → imaging
  - Size and Morphology
- PET and New MR techniques
- Incidence of PLNM (prostate cancer LN metastases) is increasing in last decade → in men 75 years old or older
- This despite overall decrease in the incidence of prostate cancer → raises concern for an increase in disease severity at presentation in the current era

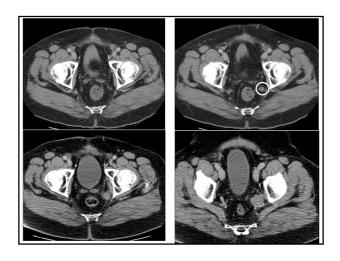
J Urol. 2018;199(6):1510-7

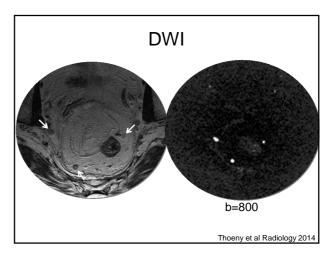


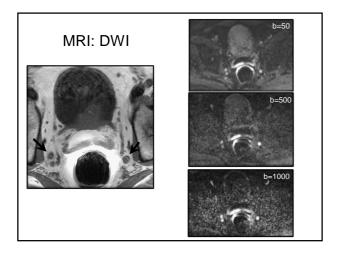


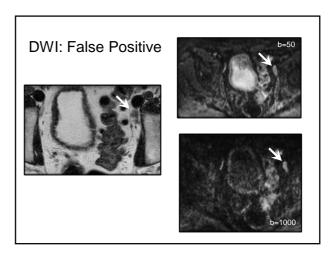










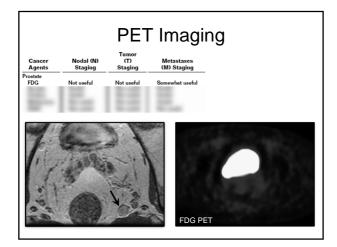


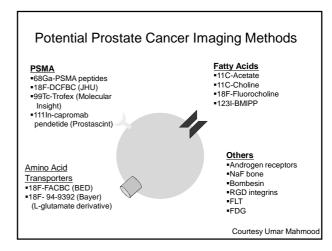
### PET Tracers for Nodal Staging

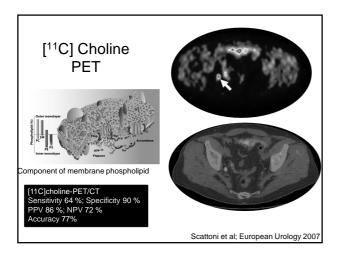
### **FDG PET**

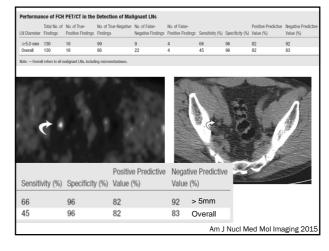
 Low FDG avidity of most prostate cancer cells and urinary activity are suggested as the main limitations of <sup>18</sup>F FDG PET in the evaluation of patients with prostate cancer

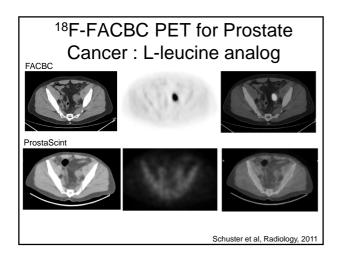
Effert et al. J Urol 1996

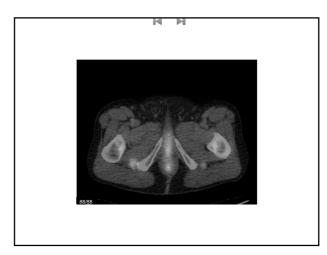


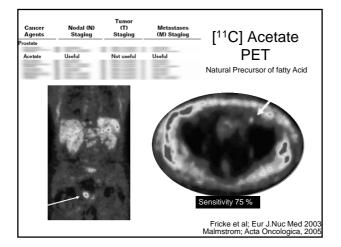


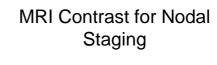


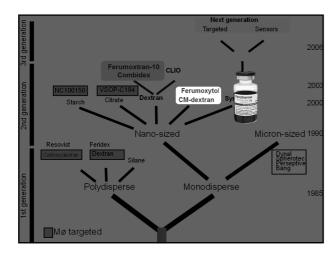


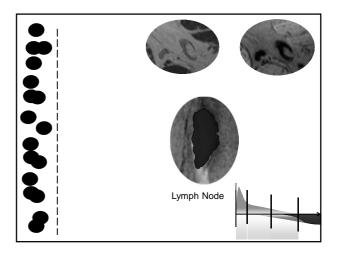


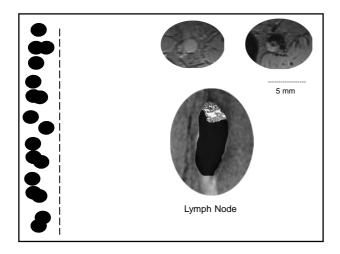


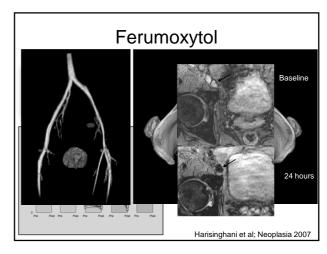


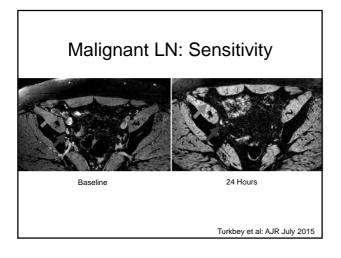


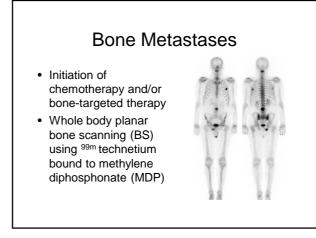


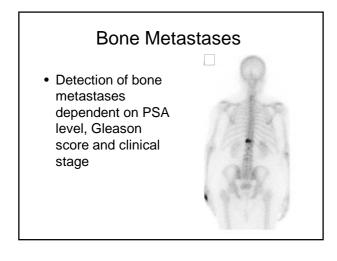


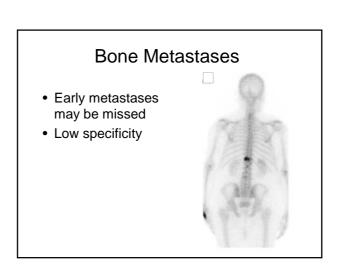


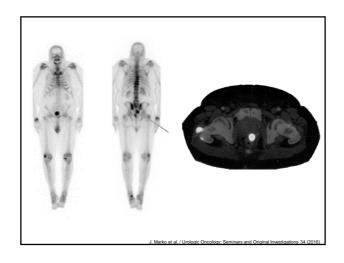








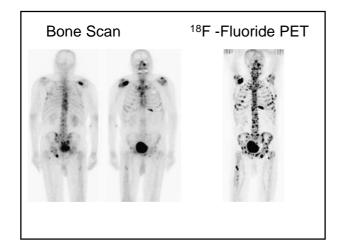


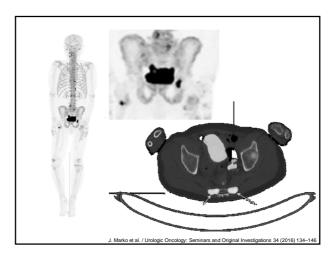


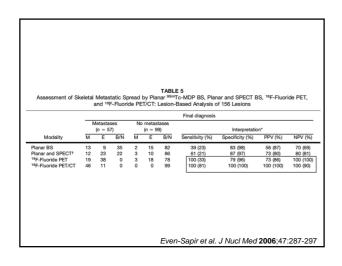
### **Bony Metastases**

- ¹8F -Fluoride PET imaging → high sensitivity for detecting bone metastases
- Mechanism
  - -increase in regional blood flow
  - -Increase bone turnover
- Lower protein biding than MDP

Even-Sapir et al. J Nucl Med 2006;47:287-297









* Reference in	nageSensitivity	Specificity	Accuracy	AUC
BS	62 (p<0.001)	98 (p=0.32)	90	0.80 (p<0.001
SPECT	74 (p < 0.01)	94 (p $<$ 0.01)	89	0.83 (p < 0.01)
SPECT/CT	85 (p = 0.05)	99 $(p = 0.32)$	96	0.92 (p = 0.24)
PET/CT	93 (*)	99 (*)	98	0.96 (*)
wbMRI+DWI	91 $(p = 0.65)$	99 $(p = 0.32)$	97	0.95 (p = 0.92)

### **Take Home Points**

- Conventional Imaging limited in ability to stage nodes
  - LNMRI and emerging PET tracers will add value
- BS standard of practice of bony metastases
  - Small lesions and specificity
  - Sodium Fluoride PET and Choline PET

### Prostate MRI for Evaluation of Prostate Cancer: An Overview of Techniques and Interpretation

Leo L Tsai, MD PhD MSc Director of Oncologic Imaging Director of Genitourinary Imaging Beth Israel Deaconess Medical Center Harvard Medical School Boston, MA



No Relevant Disclosures

### Outline

- Equipment
- Pulse Sequences
- Prostate Cancer Detection • PI-RADS
- Prostate Cancer Staging

### Equipment: 1.5 T vs 3.0 T systems

- 3.0 T is preferred
  - Improved signal/resolution
- 1.5 T systems may offer more open designs
- < 1.5 T is not recommended



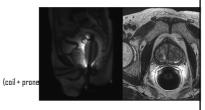
### Equipment: Endorectal coil

### ${\sf Advantages}$

- Provides signal boost
- Can improve resolution
- May be required for 1.5 T

### Disadvantages

- Discomfort
   nosition)
  - osition)
- Workflow
- Distortion may preclude mapping for US fusion or radiotherapy



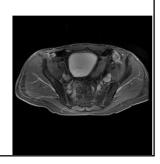


### MRI protocol

- Protocols can vary

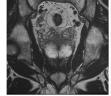
- Other Sequences:
  - TI-Weighted sequence
    Dynamic Contrast Enhancement

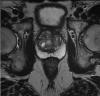
  - MRI Spectroscopy
     Large field of view pelvis



### T2 Weighted Sequences

- "Anatomical Sequence"
- T2 hyperintense (bright)
   Fat (can be suppressed)
   Fluid
   Prostate peripheral zone





### Diffusion Weighted Sequences and ADC

- Detects slow water motion ("restricted diffusion")
- Lesions with high cellularity
- Sensitive for tumors and lymph nodes
- Apparent Diffusion Coefficient (to exclude T2 effect)
- Tumors are DWI "bright", ADC "dark"







### TI Weighted Sequences

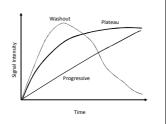
- T1 hyperintense (bright)
- Blood
- Fat (can be suppressed)
- IV Contrast
- T1 hypointense (dark)
  - Fluid Fibrosis

  - Calcifications
  - Cortex



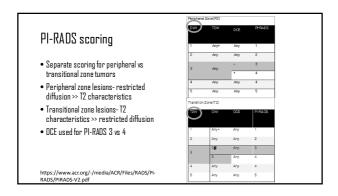
### Dynamic Contrast Enhancement

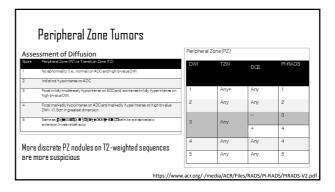
- Pre- and post-contrast images obtained
- Multiple phases obtained
- Focus on arterial enhancement and delayed venous phases
- Tumors: arterial hyperenhancement with venous washout

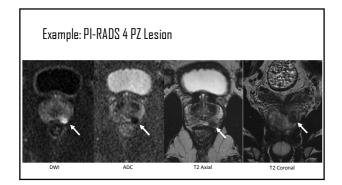


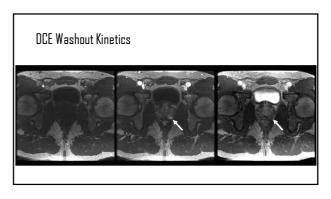
### Prostate Imaging - Reporting and Data System (PI-RADS, version 2, 2015)

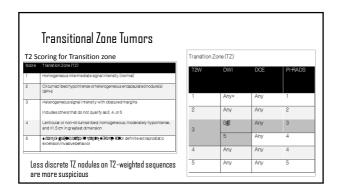
- $\bullet \ \mathsf{PIRADS} \ \mathsf{1} \mathsf{Very} \ \mathsf{low} \ \mathsf{(clinically significant cancer}^* \ \mathsf{is} \ \mathsf{highly} \ \mathsf{unlikely} \ \mathsf{to} \ \mathsf{bepresent)}$
- PIRADS 2 Low
- PIRADS 3 Intermediate (equivocal)
- PIRADS 4 High
- PIRADS 5 Very high (highly likely to be present)
- \*Gleason score ≥7 (including 3+4 with prominent but not predominant Gleason 4 component), and/orvolume ≥0.5cc, and/or extra prostatic extension (EPE)

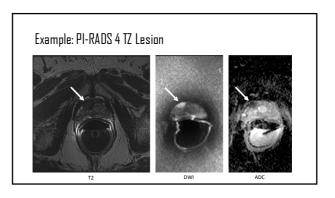








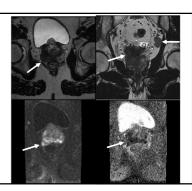




## Example: BPH Nodule

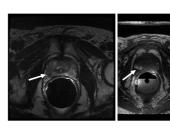
### Staging

- Look for extraprostatic extension
- Capsular bulging
- Neurovascular contact/encasement
- Lymphadenopathy
- Post-contrast images can be helpful



### Pitfalls

- Exophytic BPH nodules
- Stromal Tissue
- Prostatitis
- Hemorrhage
- Post-treatment changes



### Summary

- $\bullet$  MRI equipment and techniques can vary from site to site
- Pulse sequence design is as important as equipment
- Be aware of potential technical limitations
- Peripheral and transitional zone tumors are detected differently
- PI-RADS template is now widely accepted
- Talk to your radiologists!

### Scrotal Ultrasound

Aoife Kilcoyne, MB BCh BAO

### **Disclosures**

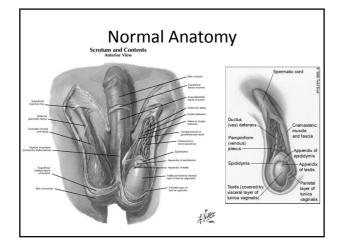
• I have no disclosures

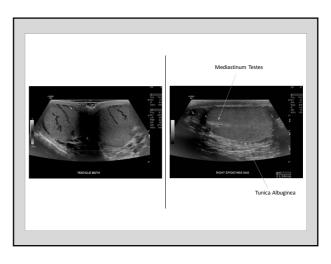
### **Learning Objectives**

- US technique
- Normal anatomy
- Acute
  - Testicular torsion
  - Epididymo-orchitis
- Non acute
  - Varicocele
  - Testicular masses: benign/malignant
  - Extra-testicular masses

### Technique

- Supine position
- High resolution transducer 10-14 Mhz
- Supine patient
- Legs slightly apart
- Towel under testes
- Images: transverse, sagittal images testes, epididymis, both testes color Doppler, pulsed wave Doppler



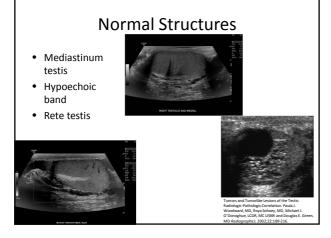


### **Contents of Spermatic Cord**

- Testicular artery
- Testicular veins (pampiniform plexus)
- Testicular lymph vessels
- Autonomic nerves
- Remains of processus vaginalis
- Vas deferens
- Cremasteric artery (branch of the inferior epigastric)
- Artery of vas deferens (branch of inferior vesical)
- Genital branch of genitofemoral nerve (L1-L2)

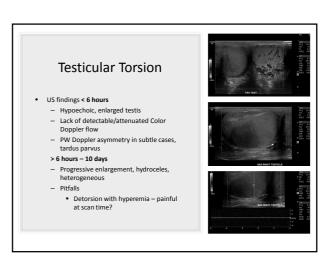
### **Blood Supply of the Testis**

- Testicular artery originates from aorta
- Deferential artery originates from the superior vesical artery
- Cremasteric artery originates from inferior epigastric artery





# Testicular Torsion • Surgical emergency - Surgery within: • 6 hours – 80% salvage • 12 hours – 70% salvage • > 12 hours – 20% salvage - Etiology • Bell clapper anomaly



### Epididymitis and epididymo-orchitis

- Most common cause of the "acute scrotum"
- Young men: GC, Chlamydia
- Older men: G –ve organisms
- Mumps uncommon
- US findings: enlargement, hypoechoic, hyperemic. Orchitis – begins adjacent to epididymis, spreads



Avery et al, Radiographics, 2013

### Non-Acute

### **Scrotal Mass**

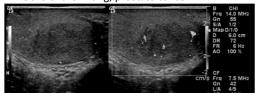
- Decision:
  - Intratesticular or extratesticular
- Intratesticular
  - Most cancers are hypoechoic. But necrosis, hemorrhage can produce hyperechoic foci
  - Sonographic appearance not specific
  - All intratesticular masses should be considered malignant until proven otherwise

### Scrotal Mass Contd.

- Ultrasound is highly sensitive for detection of intratesticular masses ~98%
- Primary testicular neoplasms
  - − ~ 95% germ cell tumors most malignant
    - Seminoma 50%
    - Embryonal cell carcinoma 25%
    - Teratomas 10%
    - Choriocarcinoma 3%
    - Yolk sac tumors (60% in infants)
  - ~ 5% stromal Sertoli or Leydig cell tumor most benign

### Scrotal Mass Contd.

- Secondary testicular neoplasms
  - Lymphoma (especially older men)
    - The most common bilateral testicular tumor
  - Leukemia (sanctuary site)
  - Others rare lung, prostate cancer



### Benign Testicular Masses

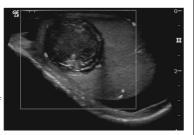
- Tunica albuginea cysts – peripheral, 2-5 mm, simple
- Ectasia of the rete testis





### **Benign Testicular Masses**

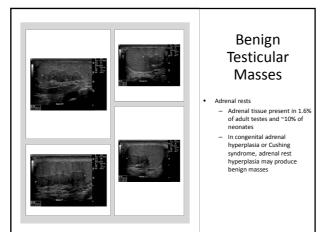
- Epidermoid cyst
  - Layered appearance
  - Not entirely specific
  - Imaging may prompt testiclesparing surgery esp. in setting of infertility



### Benign Testicular Masses

- Tecticular abscess
- Irregular
- Increased through transmission of sound
- Peripheral hyperemia
- +/- skin thickening





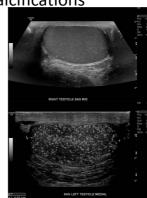
### Benign Testicular Masses

- Testicular Infarction
  - Torsion, trauma, emboli, vasculitis, sickle cell disease, leukemia
  - Well defined, avascular, painful
  - Can confirm with MRI
     urology referral,
     close observation
     mandatory
- Sarcoid



### **Testicular Calcifications**

- Testicular microlithiasis
  - Etiology unknown
  - Associated with germ cell tumors
  - Value of follow up imaging questionable, variably followed up at different institutions.



### **Testicular Calcifications**

- Coarse calcifications
  - Dystrophic
    - Calcified hematoma
    - Burnt out tumor
    - Sertoli cell tumor large cell variant, echogenic masses

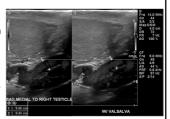
### Varicocele

- Abnormal dilation of the veins of the pampiniform plexus
  - Primary (idiopathic)
  - Secondary (proximal obstruction)
    - New varicocele in a patient > 40 years warrants CT abdomen



### Varicocele

- Three grades (clinical) 1 – palpable with Valsalva 2 – without Valsalva
- 3 Visible
- US criteria
  - Multiple veins (? > 3)
- > 3mm, but > 5 mm more likely significant
- Reversal of flow after Valsalva prolonged reversal (> 2 sec) significant
- Short reversal (< 1 sec) physiologic



### Varicocele

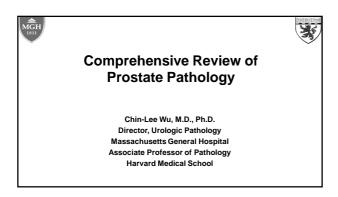
- Fertile asymptomatic men clinical varicocele present in up to 15% and reversed flow with Valsalva in 25%
- Varicocele is a major contributor to male infertility but sonographic findings do not correlate well with severity of disease

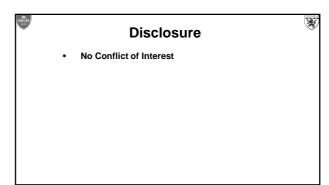
### Extratesticular Mass

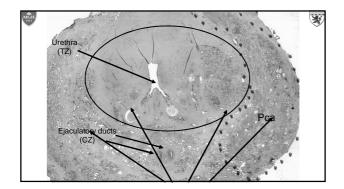
- Benign more common
- Lipoma most common
- - Lipoma, liposarcoma, angiomyofibroblastoma (AMF)
- Enhancing soft tissue + fat:
  - Liposarcoma, AMF
- Fibrous
  - Fibrous pseudotumor

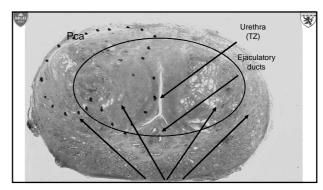
Wolfman et al, Radiographics, 2015

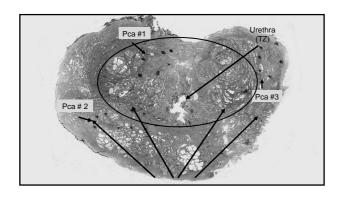
### Thank you

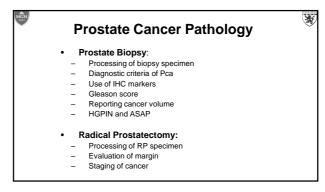


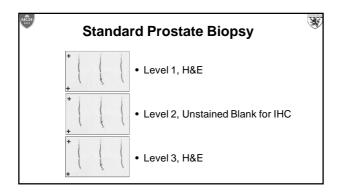


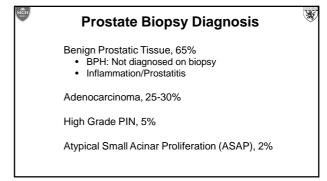


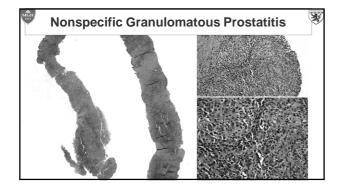


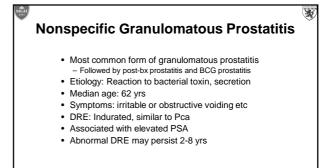


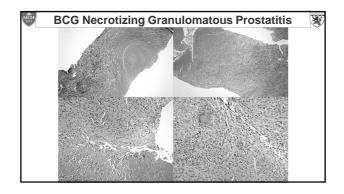


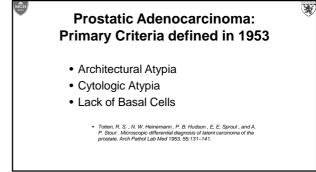


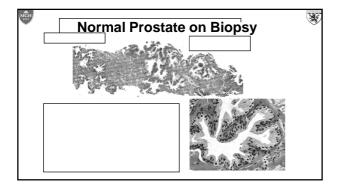


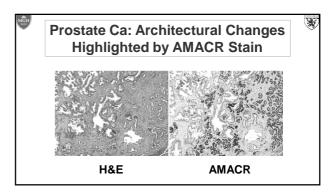


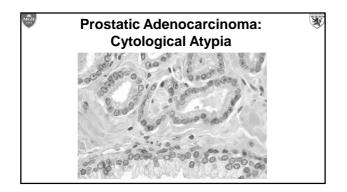




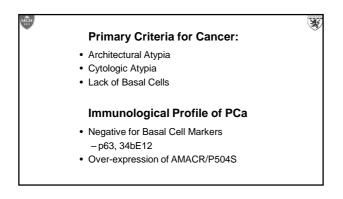


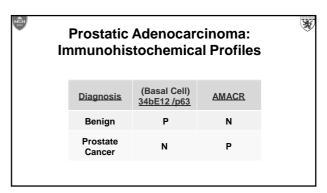


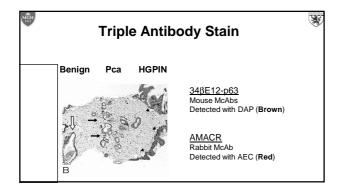


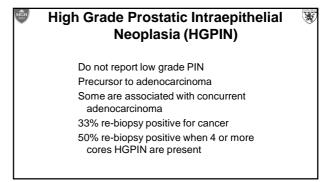


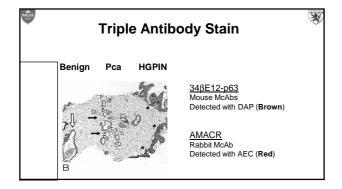


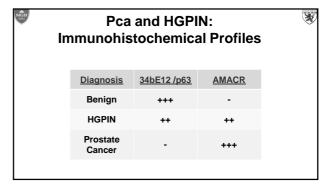


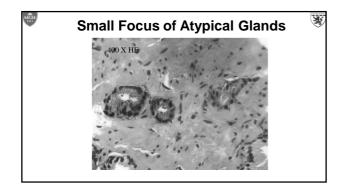


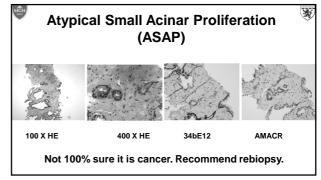












### Pathologic Findings in Determining Eligibility for Active Surveillance Consensus and Recommendation from CAP, ISUP, ADASP, NZSP and PCF

CAP: College of American Pathologists
ISUP: International Society of Urologic Pathology
ADASP: Asso. of Directors of Anatomical and SP
NZSP: New Zealand Society of Pathology
PCF: Prostate Cancer Foundation

Amin. MB et al Arch Pathol I ab Med. 2014: 138:1387-1405

### Reporting of Positive Biopsy Cores for Active Surveillance

- Histologic Type
- Number of Positive Cores
- · Location of Positive Cores
- Tumor Quantification (% or mm)
- Gleason Scores
- · ASAP on Separate Cores
- Other Findings (report only if present):
  - Extraprostatic Extension (EPE)
  - Perineural Invasion (PNI)

Amin MR et al Arch Pathol I ah Med 2014: 138:1387-1405

### Tumor Extent on Biopsy Recommendation from CAP, ISUP, ADASP, NZSP and PCF # of positive cores / total # of cores Linear % of cancer in the involved core (not area) (eg. 10%, comment if core < 6 mm) and or Linear length mm of cancer and total core length

• (eg. 1.5 mm involved in a 15 mm core)



Amin, MB et al Arch Pathol Lab Med. 2014; 138:1387-1405

### MGH Reporting Format (for each block)

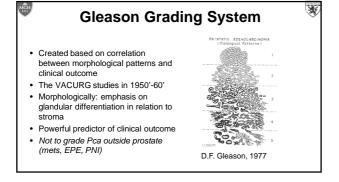
• Prostatic adenocarcinoma

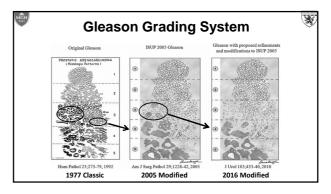
• Gleason Score: 3+3 (Grade group 1)

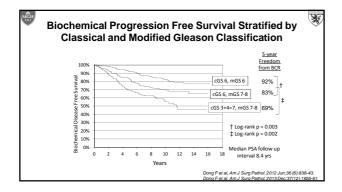
• Number of cores involved: 2 of 2

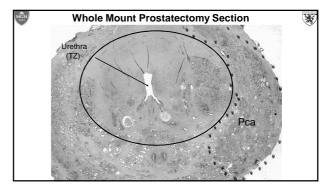
 Percentage and length involved by cancer: 10%, 2 mm; <5%, <0.5 mm</li>

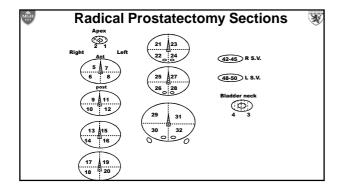
• Perineural invasion is: present

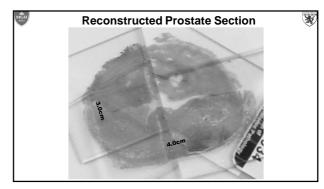


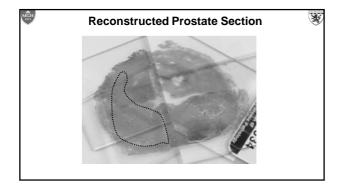


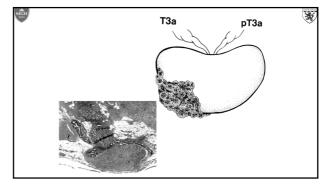


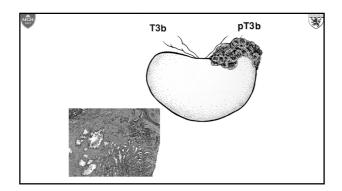


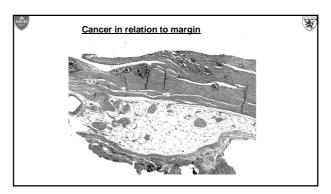


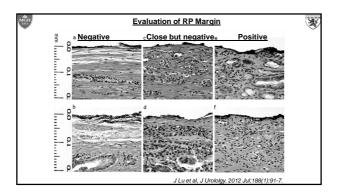


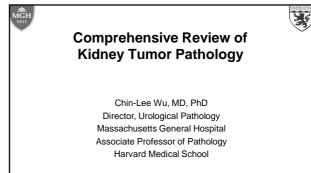






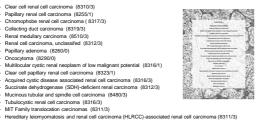






### Tumors of the Kidney (2016 WHO)

- Clear cell renal cell carcinoma (8310/3)
   Papillary renal cell carcinoma (8255/1)
   Chromophobe renal cell carcinoma (8317/3)
   Collecting duct carcinoma (8319/3)
   Renal medullary carcinoma (8510/3)
   Renal cell carcinoma, unclassifed (8312/3)



### Tumors of the Kidney (2016 WHO)

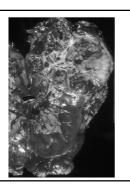
- Traditional RCCs:
   Clear cell renal cell carcinoma (8310/3)
   Papillary renal cell carcinoma (8255/1)
   Chromophobe renal cell carcinoma (8317/3)
   Collecting duct carcinoma (8319/3)
   Renal medullary carcinoma (8510/3)
   Renal cell carcinoma, unclassified (8312/3)

- Traditional Benign Tumors.
   Papillary adenoma (8260/0)
   Oncocytoma (8290/0)
   Newly Accepted Low Grade RCCs
   Multicoutar cystic renal neoplasm of low malignant potential (8316/1)
   Clear cell papillary renal cell carcinoma (8323/1)
   Clear cell papillary renal cell carcinoma (8323/1)
   Succinate dehydrogenase (SDH)-deficient renal carcinoma (8316/3)
   Succinate dehydrogenase (SDH)-deficient renal carcinoma (8310/3)
   Tubulocystic renal cell carcinoma (8316/3)
   Newly Accepted High Grade RCCs
   MiT Family translocation carcinomas (8311/3)
   Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associe ma (HLRCC)-associated renal cell carcinoma (8311/3)

### RCC, Clear Cell Type

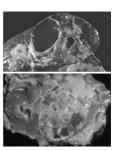
- Most are solitary
- · Multiple often associated with von Hippel-Lindau disease
- · Rounded, bosselated
- Non-encapsulated
- Pushing margin
- Golden-orange due to rich lipid content:
   Cholesterol

  - Neutral lipidsPhospholipids
- Associated with necrosis, cystic degeneration, hemorrhage and calcification.



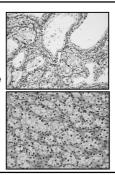
### RCC, Clear Cell Type

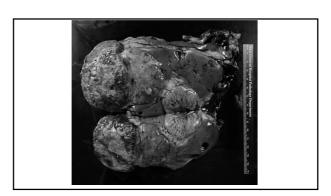
- Multiple often associated with von Hippel-Lindau disease.
- · Rounded, bosselated
- · Non-encapsulated
- Pushing margin
- Golden-orange due to rich lipid content:
  - CholesterolNeutral lipids
  - Phospholipids
- Associated with necrosis, cystic degeneration, hemorrhage and calcification.



### Clear Cell RCC

- Delicate interconnecting vasculature
- Compact and tubulocystic architecture
- Clear cytoplasm
- Low nuclear/cytoplastic ratio
- Can have eosinophilic granular cytoplasm

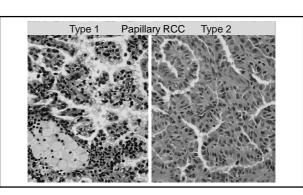




### Papillary Renal Cell Carcinoma

Gray-tan Well circumscribed 2-18 cm (mean 7cm) 75% at poles 40% multiple



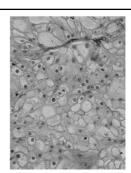


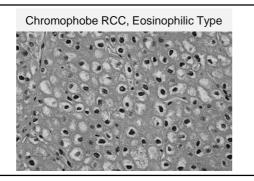
### Chromophobe RCC Gray, beige Well circumscribed

### Chromophobe RCC, Conventional Type

- Compact architecture
- Large sheets mosaic pattern
- Large cells
- Prominent cytoplasmic membrane ("plant-like")
  Pale flocculent cytoplasm
  Perinuclear halo

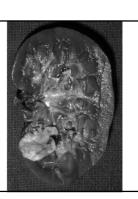
- Wrinkled nuclear contours
- · Hyperchromatic nuclei
- Binuclear cells
- · Mixed with eosinophilic cells





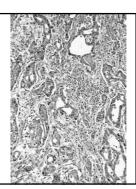
### Collecting Duct Carcinoma

- 1-2% of renal tumors
- 2/3 cases symptomatic
- 80% have nodal mets
- Wide age group
- Deep medulla
- · Infiltrative borders



### Collecting Duct Carcinoma

- Branching tubules
  Desmoplastic stroma,
  neutrophils
  Cords, papillae, microcysts
  Eosinophilic cells, prominent
  nucleoli, hobnail, focal mucin
  Dysplasia nearby collecting
  ducts



### **Unclassified RCC**

- · Not a distinct entity
- Tumors do not fit into any of the recognized entities
- Could be low grade or high grade

### Tumors of the Kidney (2016 WHO)

- Traditional RCCs:
   Clear cell renal cell carcinoma (8310/3)
   Papillary renal cell carcinoma (8250/3)
   Carcinomo (8250/4)
   Collecting duct carcinoma (8319/3)
   Collecting duct carcinoma (8319/3)
   Renal medullary carcinoma (8510/3)
   Renal cell carcinoma, unclassifed (8312/3)
- Traditional Benign Tumors:
   Papillary adenoma (8260/0)
   Oncocytoma (8290/0)

- Newly Accepted Low Grade RCCs

   Multiocular cystic renal neoplasm of low malignant potential (8316/1)

   Clear cell papillary renal cell carcinoma (8323/1)

   Clear cell papillary renal cell carcinoma (8323/1)

   Acquired cystic disease associated renal cell carcinoma (8316/3)

   Succinate dehydrogenase (SDH)-deficient renal carcinoma (8312/3)

   Mucinous tubular and spindle cell carcinoma (848/0/3)

   Tubulocystic renal cell carcinoma (8316/3)

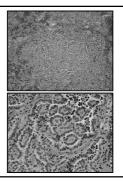
  4. Newly Accepted High Grade RCCs

   MIT Family translocation carcinomas (8311/3)

   Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma (8311/3)

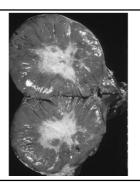
### Papillary Adenoma

- Diameter ≤ 1.5 cm (previously 0.5 cm)
- Unencapsulated mass
- · Histologically indistinguishable from low grade papillary RCC



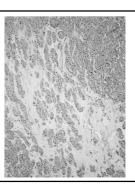
### Oncocytoma

- 5-9% of renal tumors
- Mahogany brown
- Well circumscribed
- 50% central stellate myxoid fibrosis
- Some large, >15 cm
- 5% bilateral/multifocal



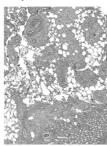
### Oncocytoma

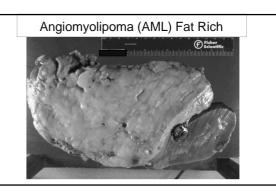
- · Compact or nested
- Fine granular cytoplasm
- Round, small nuclei
- Often prominent nucleoli
- Nuclear pleomorphism "bizarre cells" in 10%

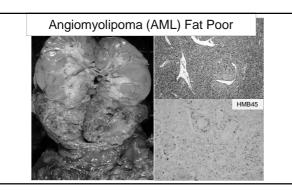


### Angiomyolipoma (AML)

- 3 components:
- Dysmorphic think wall blood vessels
- Spindle smooth muscle cells, can be epithelioid - Adipose cells
- Associated with tuberous sclerosis complex (TSC) or sporadic
- Benign, risk of bleeding/rupture
- Cell origin: Perivascular epithelioid cells (PEComas)
- IHC
  - HMB-45+, Melan A +, Vimentin+, Actins+
  - Adipocyte S-100+ Keratin-, EMA-







### Tumors of the Kidney (2016 WHO)

- Traditional RCCs:
   Clear cell renal cell carcinoma (8310/3)
   Papillary renal cell carcinoma (8255/1)
   Chromophobe renal cell carcinoma (8317/3)
   Collecting duct carcinoma (8319/3)
   Renal medullary carcinoma (8510/3)
   Renal cell carcinoma, unclassifed (8312/3)
- Traditional Benign Tumors:
   Papillary adenoma (8260/0)
   Oncocytoma (8290/0)

- Newly Accepted Low Grade RCCs

   Multiocular cystic renal neoplasm of low malignant potential (8316/1)

   Clear cell papillary renal cell carcinoma (8323/1)

   Clear cell papillary renal cell carcinoma (8323/1)

   Acquired cystic disease associated renal cell carcinoma (8316/3)

   Succinate dehydrogenase (SDH)-deficient renal carcinoma (8312/3)

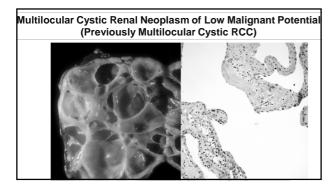
   Mucinous tubular and spindle cell carcinoma (840/3)

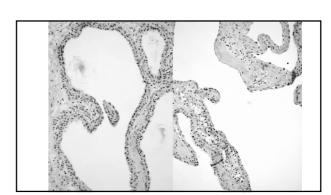
   Tubulocystic renal cell carcinoma (8316/3)

  4. Newly Accepted High Grade RCCs

   MIT Family translocation carcinomas (8311/3)

   Herediary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma (8311/3)





### Clear-Cell Papillary RCC

- Adult Population, 1-5% of Renal
- Tumors Indolent Course
- Small (Mean size 2.4 cm)
- Often Cystic with Fibrous Capsule and Stroma
   No Gain of Chrom 7, 17 or Loss of Y
- (Not PRCC) No Del of 3p, VHL Mutations, or VHL
- Promoter Hypermethylation (Not CC-RCC)





### Acquired Cystic Disease (ACD)-Associated RCC

- Most common RCC in end stage kidney disease & acquired cystic disease
   36% of dominant mass in end stage kidney

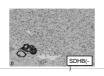
  - 46% of dominant mass in acquired cystic diseases
- · Multifocal, bilateral
- · Well circumscribed, associated with cysts
- Main features
  - Cribriform, sieve-like structure
  - Eosinophilic cytoplasm (often mistaken for PRCC type 2), Grade 3 nuclei
  - Intratumoral oxalate crystals

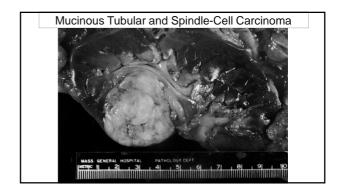


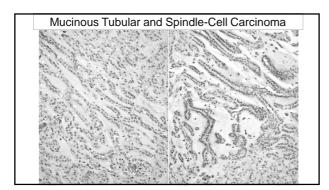
### Succinate dehydrogenase (SDH)-deficient RCC

- he most distinctive feature is the presence of cytoplasmic vacuoles
- IHC is a useful tool for their diagnosis because there is a loss of expression of SDHB
- It presents mainly in young adults, and most patients have germline mutations in an SDH gene
- Most SDH-deficient RCC has good prognosis









### Tubulocystic RCC

- >90% indolent course
- M:F >7:1
- Incidental complexed cyst on
- Sponge-like gross appearance
- Grade 3 nuclear features



### Tumors of the Kidney (2016 WHO)

- Lumors of the Kidney (2016 WHO)

  1. Traditional RCCs:

   Clear cell renal cell carcinoma (8310/3)

   Papillary renal cell carcinoma (8310/3)

   Papillary renal cell carcinoma (8317/3)

   Colineting duct carcinoma (8319/3)

   Renal medillary carcinoma (8519/3)

   Renal cell carcinoma, unclassified (8312/3)

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   Papillary adenoma (8260/0)

   Oncoporoma (8290/0)

  3. Newly Accepted Low Grade RCCs

   Multilocular cysts renal neoplasm of low malignant potential (8316/1)

   Clear cell papillary renal cell carcinoma (8323/1)

   Acquired cystic desaste associated renal cell carcinoma (8316/3)

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   Tubulocystic renal cell carcinoma (8316/3)

   Tubulocystic renal cell carcinoma (8316/3)

   Newly Accepted High Grade RCCs

   MIT Family translocation cerinomas (8311/3)

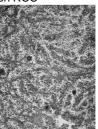
   Herediary leiomyonatosis and renal cell carcinoma (HLRCC)-associated renal cell carcinoma (8311/3)

### MiTF Family Translocation RCC

- Xp11.2 Translocation TFE3 Gene - Fusion of TFE3 with PRCC, ASPL etc
- t (6;11)(p21;q12)
  - Alpha-TFEB gene fusion

### Xp11 Translocation RCC

- 50% of RCC in children and young adults
- Recently described in broad adult age range
- 1-4% adult RCC
- Female predominance: 22:6
- · Clinical behavior unclear: possibly aggressive in adults



### Hereditary leiomyomatosis and renal cell carcinoma (HLRCC)-associated renal cell

- · Are rare tumors occurring in the setting of non-renal leiomyomatosis and show germline mutation
- The diagnosis of HLRCC-associated RCC:
  - is made when the characteristic morphological features are identified in the tumor.
  - is confirmed by the presence of germlie mutations in *FH* (the gene encoding fumarate hydratase), at 1q42.3-q43.





### **Grading and Staging**

### Grading of Renal Tumours

- Many grading systems have been proposed for renal cell neoplasia.
  - The Fuhrman system was the most frequently used grading system in RCC but should not be applied for chromophobe RCC.
    - Furthermore, the Fuhrman system has NOT been validated for most of the new subtypes of renal carcinoma.
  - For these reasons, the four-tiered WHO/ISUP grading system is recommended by the WHO

### WHO / ISUP Grading System for CCRCC and Papillary RCC

### Description Nucleoli are absent or inconspicuous and basophilic at ×400 magnification. Nucleoli are conspicuous and eosinophilic at $\times 400$ magnification and visible but not prominent at $\times 100$ magnification. Grade 3 Nucleoli are conspicuous and eosinophilic at ×100 magnification. There is extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid and/or sarcomatoid differentiation.

### pT Staging of RCC (AJCC TNM 8 ed. 2017)

Confined to the kidney =< 7 cm

T1a: =<4 cm

T1b: >4 cm, =<7 cm Confined to the kidney, >7 cm

T2a: 7 - 10 cm

T2b: >10 cm

120: >10 cm
Tumor extending a major vein or perinephric fat, but not into the ipsilateral
adrenal gland or beyond Gerota's fascia.

T3a: tumor extending into the renal vein or its segmental branches, or tumor
invading the pelvicalyceal system or tumor invading perirenal and/or renal
sinus fat (peripelvic fat), but not beyond Gerota's fascia

T3b: tumor growing into vena cava below diaphragm.

T3c: tumor growing into vena cava above the diaphragm or into the wall of the vena cava.

Tumor invading beyond Gerota's fascia including contiguously extension into the ipsilateral adrenal gland

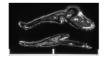
pT Staging of RCC (AJCC TNM 8<sup>th</sup> Ed. 2017) pT3a:

- Word "grossly" was eliminated from the description of renal vein involvement
- "Muscle containing" was changed into "segmental veins"
- Invasion of the pelvicalyceal system was added



### Comprehensive Review of Adrenal Gland Pathology

Chin-Lee Wu, M.D., Ph.D.
Director, Urologic Pathology
Massachusetts General Hospital
Associate Professor of Pathology
Harvard Medical School



Normal Adrenal Gland: A Composite of Two Endocrine Organs

- Cortex: mesoderm derived
   Medulla: neuroectoderm derived
- Normal weight: 6 gm

## Normal Adrenal Gland Zona Glomerulosa Aldosterone Fasciculata Glucocorticoid Reticularis Sex hormone Cortex Medulla (catecholamines)

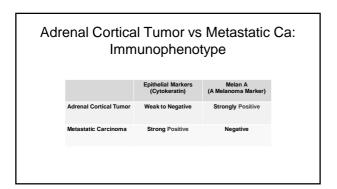
### Adrenal Gland: Diagnostic Issues

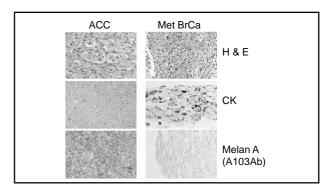
- Primary Adrenal Tumors vs Metastasis
- Adrenal Cortical Hyperplasia vs Adenoma vs Carcinoma
- Pheochromocytoma
- Neuroblastic Tumors (Neuroblastoma)
- Incidentaloma and FNA

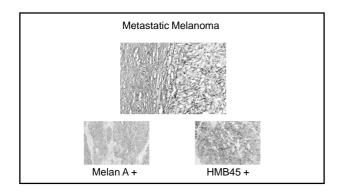
### Adrenal Gland Metastasis

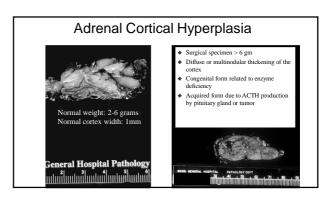
- 4<sup>th</sup> most common site of metastasis (surpassed by lung, liver and bone)
- 27% of 1000 ca. patients at time of autopsy
- 2.5% of adrenal incidentaloma
- Metastatic carcinoma
  - Breast, lung, kidney, GI, ovary,
- Melanoma
- Lymphoma

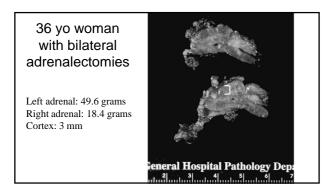
Abrams HL et al Cancer 1950; 3:74-85 Lack EE, 1997. Tumor of the Adrenal Gland and Extra-Adrenal Paraganglia, AFIP Young 2000, Endocrin. Metabol. Clin. N. America 29:159

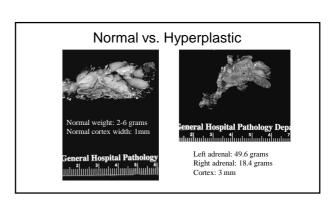












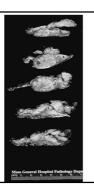
#### 36 yo woman

- What was the underlying cause of the patient's adrenal hyperplasia?
  - Pituitary hypersecretion of ACTH
  - Ectopic non-pituitary secretion of ACTH
  - latrogenic ACTH administration

#### 36 yo woman

- What was the underlying cause of the patient's adrenal hyperplasia?
  - Pituitary hypersecretion of ACTH
  - Ectopic non-pituitary secretion of ACTH, due to metastatic lung neuroendocrine tumor (carcinoid)
  - latrogenic ACTH administration

**Adrenal Cortical Adenoma** 



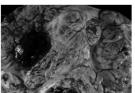
#### Adrenal Cortical Adenoma

- ◆Circumscribed, Encapsulated
- ♦Smooth
- ◆Bright or Golden Yellow
- ◆No Necrosis or Hemorrhage

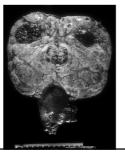




#### Adrenal Cortical Carcinoma

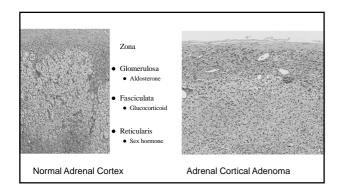


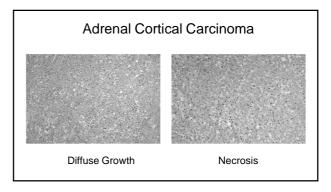
- ◆ Poorly Defined, Invasive
- ♦ Bulky, Coarse, Nodular
- $\blacklozenge$  Yellow, Tan, Brown
- ◆ Necrotic and Hemorrhagic

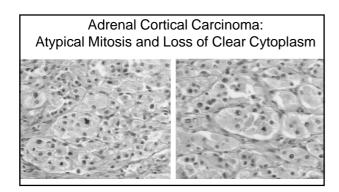


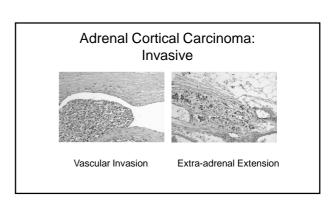
## Adrenocortical Ca vs Adenoma: Weight

Clinically Benign Malignant
Tumor < 50 gm 95% 5%
Tumors > 100 gm 5% 95%









#### Weiss' 9 Histologic Features

- 1. High Mitotic Rate (>5/50 hpf)
- 2. Atypical Mitosis
- 3. Venous Invasion
- 4. High Nuclear Grade (Fuhrman Grade 3-4)
- 5. Lack of Cells with Clear Cytoplasm (<25%)
- 6. Diffuse Growth Pattern (>1/3 of the Tumor)
- 7. Necrosis
- 8. Sinusoidal Invasion
- 9. Capsular Invasion

Weiss, Am J Surg Pathol 8:163-169, 1984

#### Weiss' Histologic Criteria for Adrenal Cortical Tumors

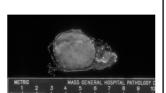
• ADENOMA of the 9 histologic features

• CARCINOMA Presence of 2 or less Presence of 3 or more of the 9 histologic features

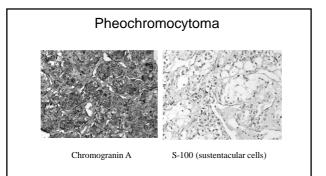
#### Pheochromocytoma

- Described in 1905 by Poll of the dusk (pheo) color (chromo) tumor exposed to dichromate
- 8/106 person-years in the U.S.
- " 10% Rule "

  - Extra adrenal Hereditary / bilateral
  - Pediatric group Malignant potential (2-14%)
- Non hypertensive
- 2-4 cm, 50-100 gm
- Clinical presentation related to hypersecretion of catecholamine



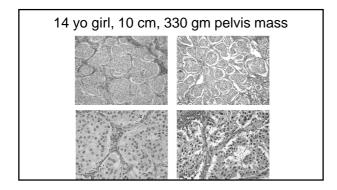
## Pheochromocytoma • Alveolar, trabecular or solid patterns Polygonal cells with moderate amount of granular, amphophilic cytoplasm Nuclear pseudoinclusion and pleomorphism Intra cytoplasmic hyaline granules Medulla

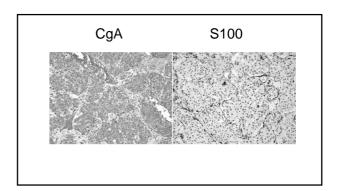


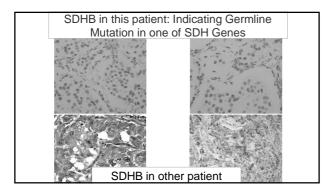
#### Pheochromocytoma: Genetic features

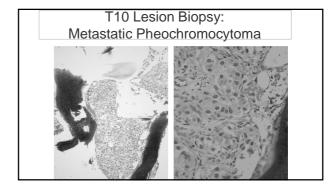
- Familial cases have mutations of proto-oncogene (RET) or genes associated with oxygen sensing pathway (VHL, SDHD, SDHB)
  - May result in activation of hypoxic signaling pathways associated with neoplastic transformation
- Germline mutations of RET, VHL, SDHD/B found in
  - ~25% of cases of sporadic pheochromocytoma

     VHL > SDHD/B > RET (Neumann et al. NEJM 2002)
- Somatic mutations in RET and VHL found in ~15% of sporadic pheochromocytomas (Eng et al. J Med Genet 1995)



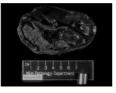






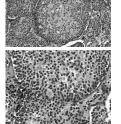
#### Neuroblastoma

- 4<sup>th</sup> most common tumor in childhood
- 90% 5 years of age of younger
- 90% Adrenal and abdominal sites



#### Neuroblastoma

- Lobular pattern with fibrovascular septa
- "small blue cell"
- Fibrillar matrix (neuritic cell process)
- Homer Wright pseudorosette
- Immunophenotype:
  - Negative for CK, MIC2
     Positive for chromogranin A
- Deletion of 1p and amplification of Myc-N gene correlated with poor outcome



#### Incidence of Adrenal Incidentaloma

- 5.9% in 87,065 autopsies in 25 studies
- Prevalence age dependent:
  - -<<1% age 0-19
  - -~0.2% age 20-29
  - -~1.5% age 30-39
  - -~ 7% age > 70
- 1 − 4 % in abdominal CT

Young 2000, Endocrin. Metabol. Clin. N. America 29:159 Barzon 2000, J Urol. 163:398

#### Adrenal Incidentaloma

- 11.4% Functioning adenoma
  - -5.3% pre-clinical Cushing's syndrome
  - -5.1% pheochromocytoma
- 1% aldosterone producing adenoma
- 82.4% non-functioning adenoma
- 4.7% adrenal corticocarcinoma
- 2.5% metastatic cancer

Young 2000, Endocrin. Metabol. Clin. N. America 29:159

#### Biopsy of Adrenal Incidentaloma





Courtesy of Dr. Mukesh Harisinghani, MGH Radiology

#### **FNA Biology**

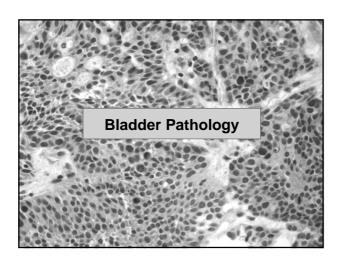
- Primary vs Metastasis
   Immunological profiles
- Adrenal Cortical Tissue
- Deciding Normal vs Hyperplasia vs Adenoma can be difficult

Correlation of Histologic, Radiologic and Clinical Findings

#### Adrenal Gland: Diagnostic Issues

- Primary Adrenal Tumors vs Metastasis
- Adrenal Cortical Hyperplasia vs Adenoma vs Carcinoma
- Pheochromocytoma
- Neuroblastic Tumors (Neuroblastoma)
- Incidentaloma and FNA





## Speaker Picture and Bio



- Surgical pathologist at Brigham and Women's Hospital with subspecialty interest in GU and **Endocrine Pathology**
- Associate Professor of Pathology at Harvard Medical School

#### **Disclosures**

- I have no financial interests to disclose

#### **Lecture Outline**

- Gross evaluation of cystectomy specimens and normal bladder anatomy and histology
- 2. Introduction to bladder carcinoma: non-muscle invasive versus invasive and papillary versus non-papillary
- 3. Non-muscle-invasive bladder tumors
  - Papillary tumors Carcinoma in situ
- 4. Muscle-invasive bladder carcinoma

  - Making the diagnosis Urothelial carcinoma variants Information included in the pathology report for cystectomy
  - Assessment of cystectomy specimens after neoadjuvant therapy Bladder tumors other than urothelial carcinoma

#### **Lecture Outline**

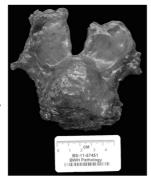
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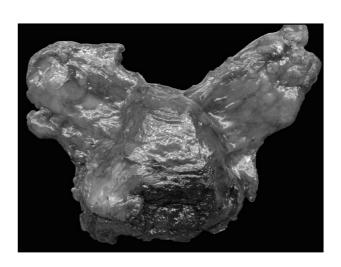
  - Papillary tumorsCarcinoma in situ
- 4. Muscle-invasive bladder carcinoma
  - Making the diagnosis
    Urothelial carcinoma variants

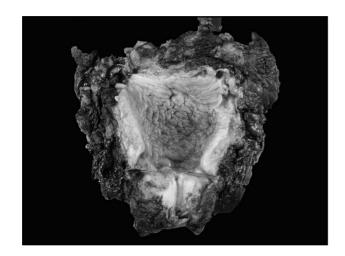
  - Information included in the pathology report for cystectomy
  - Assessment of cystectomy specimens after neoadjuvant therapy Bladder tumors other than urothelial carcinoma

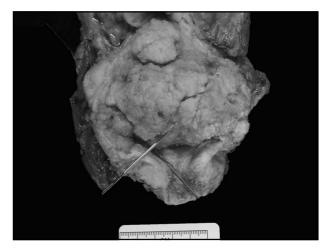
#### **Gross Evaluation**

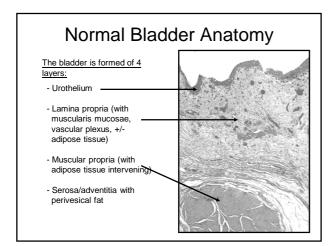
- 1. Take gross measurements (bladder, ureters, prostate with
- seminal vesicles, vagina)
  2. Ink the specimen for evaluation of margins and fix it overnight
- 3. Open the bladder along the anterior wall
- 4. Describe tumor: location, size, configuration, depth of penetration, gross margin status, etc
- 6. Submit sections:
  - A. Margins
  - B. Tumor deepest extent
  - C. Uninvolved bladder, prostate

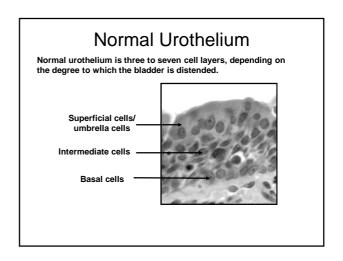












### von Brunn's Nests

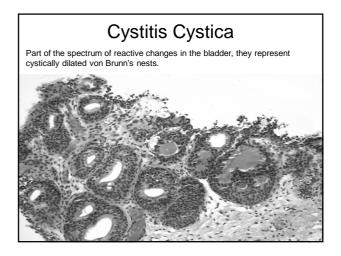
The most common variant of normal/reactive proliferative change. They represent invaginations of the surface urothelium into the underlying lamina propria.

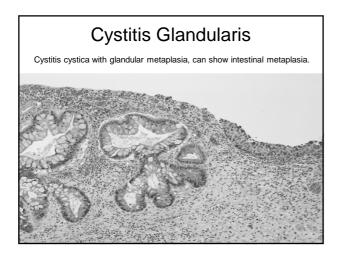
- Pitfalls:

  1. Can be hyperplastic mimicking carcinoma.
- Can misinterpret involvement of von Brunn's nests by UCa as invasion.

Have a lobular architecture, with a non-infiltrative base, lack cytologic atypia.







#### **Lecture Outline**

- 1. Gross evaluation of cystectomy specimens and normal bladder anatomy and histology
- 2. Introduction to bladder carcinoma: non-muscle invasive versus invasive and papillary versus non-papillary
- 3. Non-muscle-invasive bladder tumors

  - Papillary tumorsCarcinoma in situ
- 4. Muscle-invasive bladder carcinoma

  - Information included in the pathology report for cystectomy
  - Assessment of cystectomy specimens after neoadjuvant therapy Bladder tumors other than urothelial carcinoma

#### **Bladder Cancer**

- 90% of bladder cancers are urothelial carcinoma
- Not all urothelial carcinoma is the same
  - \*\*\*Muscle-invasive (MIBC) vs Non-muscle-invasive bladder cancer (NMIBC)
  - \*\*\*Papillary vs Non-papillary

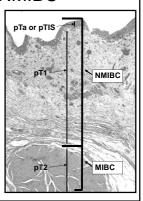
#### MIBC vs. NMIBC

Bladder cancer can be broken down into superficial/non-muscle invasive (NMIBC) and muscle invasive bladder cancer (MIBC).

NMIBC can be a papillary tumor without extension into the lamina propria (pTa), carcinoma in situ (pTis), or a tumor with invasion into the lamina propria (pT1).

NMIBC accounts for 75% of urothelial carcinomas

70% of NMIBC are pTa, 20% pT1, and 10% carcinoma in situ (CIS)



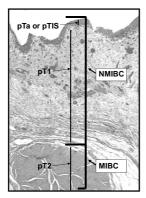
#### MIBC vs. NMIBC

#### MIBC arises from:

- CIS
- High-grade non-invasive

Progression from superficial to muscle-invasive disease occurs in only 15% of noninvasive lesions.

Only 15% have had a previous biopsy showing NMIBC, the remaining 85% are diagnosed as muscle invasive on first



#### **Lecture Outline**

- 1. Gross evaluation of cystectomy specimens and normal bladder anatomy and histology
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- 4. Muscle-invasive bladder carcinoma

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    Urothelial carcinoma variants
    Information included in the pathology report for cystectomy
  - Assessment of cystectomy specimens after neoadjuvant therapy Bladder tumors other than urothelial carcinoma

## Papillary Urothelial Tumors

Range from benign and malignant with a spectrum of changes in: thickness of urothelium, polarity, cytologic atypia, nuclear pleomorphism, mitotic activity, apoptotic cells.







## Papillary Urothelial Tumors

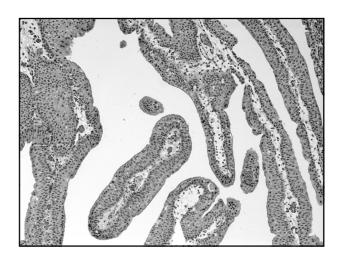
- Papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Papillary Urothelial Carcinoma, Low Grade
- Papillary Urothelial Carcinoma, High Grade

### **Papillomas**

<u>Clinical History:</u> Rare, 1-2% of papillary tumors, occur in younger patients (should be confined to patients <50 years)

#### Histology:

- Small, solitary
- Delicate finger-like non-branching papillae lined by
- Urothelium of normal thickness (3-7 cell layers)
- With normal polarization and maturation (intact superficial umbrella cells)
- Minimal cytologic atypia: atypia confined to the umbrella cells
- No mitotic figures



# Papillary urothelial neoplasia of low malignant potential (PUNLMP)

The histology is virtually the same as a papilloma though it can have slightly thicker urothelium lining the papillae.

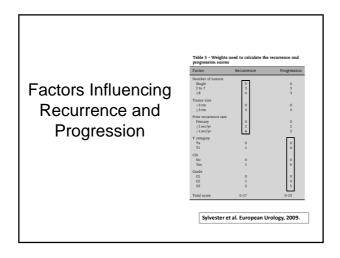
If a tumor looks like a papilloma but the patient is over 50, best to diagnose it as PUNLMP.

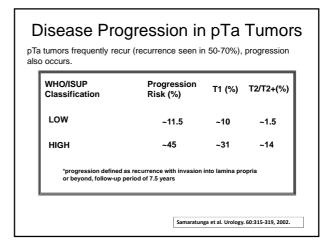
## Grading of Papillary Urothelial Carcinoma

Grading scheme important in NMIBC – once you have muscle invasion they are virtually all high grade carcinomas

Purpose of this grading system is to predict recurrence and progression.

Based on features including: polarity, cytologic atypia, nuclear pleomorphism, mitotic activity, and apoptotic cells.

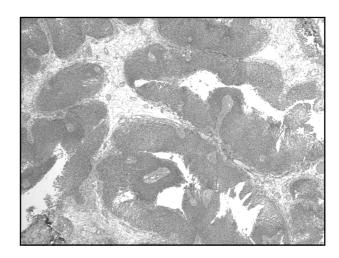


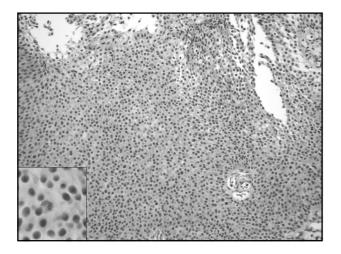


## Papillary Urothelial Carcinoma, Low Grade

#### Histology:

- Branching papillae
- Lined by urothelium >7 cell layers
- Intact polarization
- Uniform cells (may have grooved nuclei)
- Mild cytologic atypia (but more than PUNLMP),
- Low mitotic activity (limited to lower half of the urothelium)

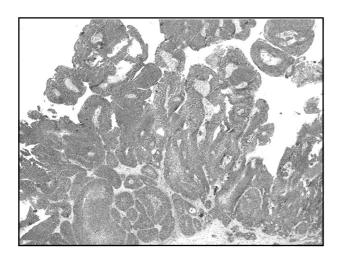


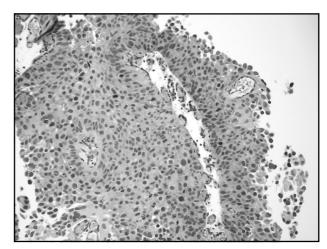


## Papillary Urothelial Carcinoma, High Grade

#### Histology:

- Branching papillae
- Lined by urothelium >7 cell layers
- Lack of polarity, disorganized architecture, discohesive
- Cellular pleomorphism moderate to marked
- Nuclear enlargement and hyperchromasia
- Frequent mitoses (throughout the layers of urothelium)



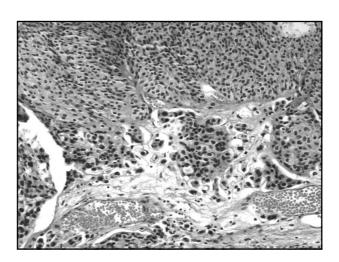


#### Lamina Propria Invasion

For NMIBC 70% are pTa, 20% pT1, and 10% carcinoma in situ (CIS).

What we see histologically: single cells, nests of cells with irregular borders, paradoxical differentiation (cells have more cytoplasm and the cytoplasm is more eosinophilic), desmoplasia, retraction artifact. Invasion into lamina propria can be the core of the papillae or at the

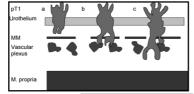
Pitfalls: tangential sectioning, obscuring inflammation, cautery artefact (significant issue resulting in interobserver variability).



### Extent of Lamina Propria Invasion

Currently we do not substage T1 tumors

AJCC recommends including a comment regarding extent of lamina propria invasion, though how to characterize extent is not established



Rhijn et al. Europ. Urol. 56:430-442, 2009.

Some studies have used invasion or muscularis mucosae.

Other studies have used depth of invasion or millimeters of invasive tumor in

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    Urothelial carcinoma variants
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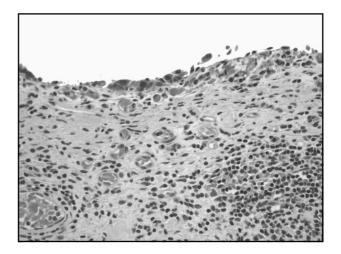
## Carcinoma In Situ (CIS)

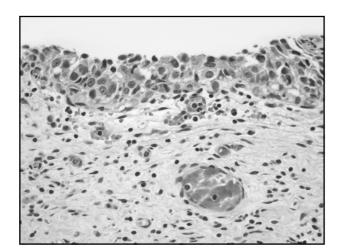
#### Urothelial Dysplasia:

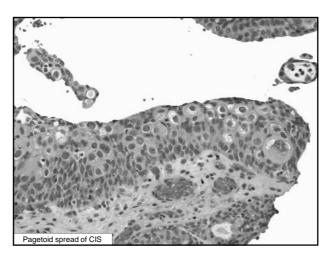
- In dysplasia the thickness is normal (<7 cells layers).</li>
  High grade dysplasia = CIS

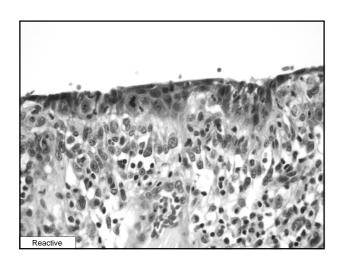
#### Histologic Features:

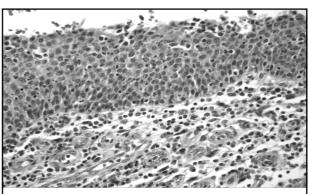
- Requires UNEQUIVOCAL severe cytologic atypia
- Enlarged hyperchromatic nuclei
- High N:C ratio (though cells retain quite a bit of cytoplasm).
- Clinging CIS: cells are dyscohesive so get sloughing
- CIS can be up to 7 cell layers thick
- Mitotic active
- Hypervascularity in the lamina propria (correlates with red areas on cystoscopy)



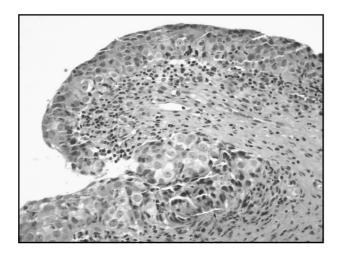








Reactive changes: tend to have vesicular chromatin with prominent nucleoli can be very mitotically active, look for acute inflammation or cause of reactive atypia.



## Immunohistochemistry for CIS

A panel with p53, CK20, and CD44 may aid in the diagnosis of CIS:

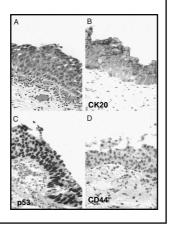
- p53 is a tumor suppressor protein. In normal urothelium p53 is negative or shows scattered weakly positive cells.
- CK20 belongs to the epithelial subgroup of cytokeratin-associated intermediate filaments. In normal urothelium, CK20 expression is confined to scattered umbrella cells
- CD44 is a transmembrane glycoprotein involved in cell-surface binding to collagen. In normal urothelium, CD44 is expressed in the basal cells.

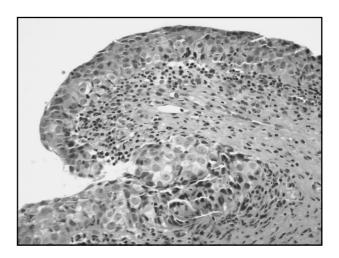
## Impox for CIS

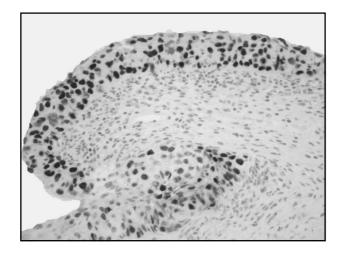
#### Study of 21 cases of CIS:

- 57% showed p53 positivity in the majority (>50%) of malignant cells.
- -81% of CIS showed intense CK20
- 56% showed reduced CD44 staining in the basal cells

McKenney et al. Am J Surg Pathol. 25(8):1074-1078, August 2001.









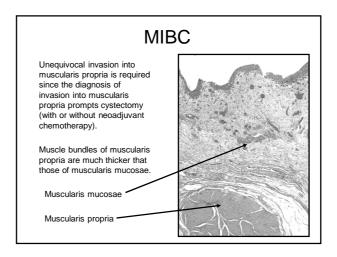
Shoulders of high grade papillary lesions can look like CIS.

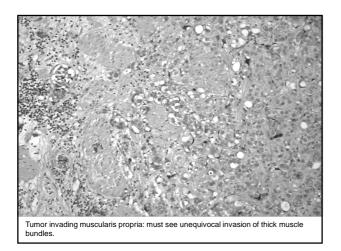
#### **Lecture Outline**

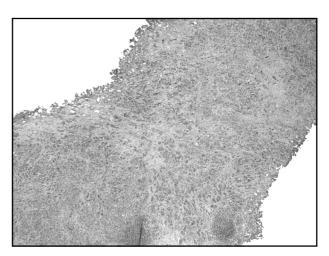
- Gross evaluation of cystectomy specimens and normal bladder anatomy and histology
- 2. Introduction to bladder carcinoma: non-muscle invasive versus invasive and papillary versus non-papillary
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   Papillary tumors
   Carcinoma in situ
- 4. Muscle-invasive bladder carcinoma

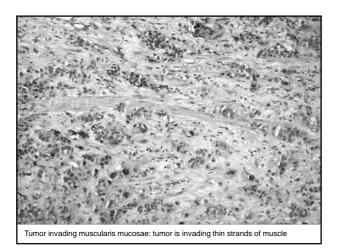
  - Making the diagnosis
    Urothelial carcinoma variants
    Information included in the pathology report for cystectomy

  - specimens
    Assessment of cystectomy specimens after neoadjuvant therapy
    Bladder tumors other than urothelial carcinoma









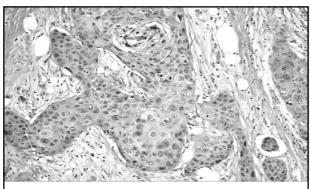
#### **Urothelial Carcinoma Variants**

Urothelial carcinoma can have variant morphology.

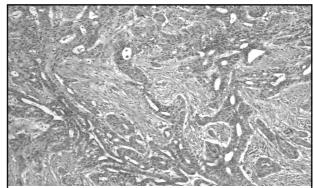
#### Variants Include:

- Squamous differentiation
- Glandular differentiation
- Micropapillary differentiation
- Nested
- Sarcomatoid differentiation

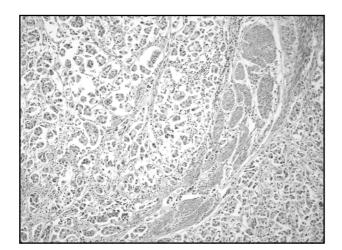
#### Copyright © Oakstone Publishing, LLC, 2018. All Rights Reserved.

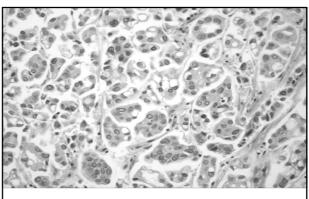


<u>Squamous differentiation:</u> seen in 20-50% of cases. Some data suggesting that it may predict a more limited response to neoadjuvant chemotherapy.

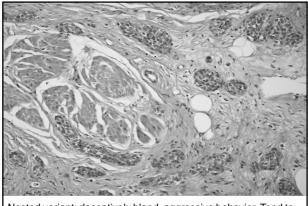


Glandular differentiation: seen in ~10% of cases. Prognostic significance and its implication for response to neoadjuvant chemotherapy is not established.

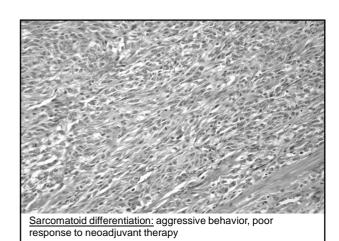




<u>Micropapillary differentiation:</u> seen in ~2% of cases. Associated with advanced stage and poor prognosis.



 $\underline{\text{Nested variant:}}$  deceptively bland, aggressive behavior. Tend to present as high-stage tumors.



#### Information in Pathology Reports for Cystectomy Specimen

What we include: Tumor type, tumor size, extent of invasion, lymphovascular invasion, margin status, lymph node status, stage

#### AJCC Stage: the most important determinant of prognosis.

Papillary tumor without invasion into lamina propria

Carcinoma in situ

Invasion into lamina propria

Invasion into superficial (inner half) of muscularis propria T2a

Invasion into deep (outer half) of muscularis propria Tumor microscopically invades perivesical tissue

T3b T4a T4b Tumor macroscopically invades perivesical tissue Tumor invades prostatic stroma, uterus, or vagina

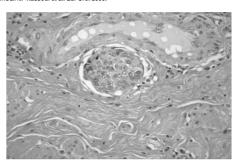
Tumor invades pelvic wall or abdominal wall Metastasis to single lymph node in true pelvis

N2 Metastasis to multiple lymph nodes in true pelvis

Lymph node metastasis to common iliac nodes

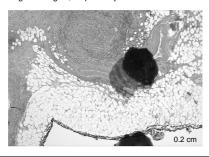
### Lymphovascular Invasion

LVI (seen in up to 40% of cases) has been shown to be prognostically



## Margin Status

Up to 4% of cases have positive margins. The 5-year cancer specific survival rates of 32 and 72% were found for patients with and without positive surgical margins, respectively. Dotan et al. J Urol 2007

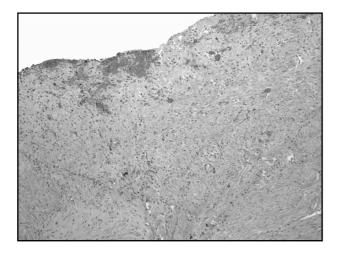


#### **Neoadjuvant Cases**

As compared with radical cystectomy alone, the use of neoadjuvant chemotherapy (M-VAC\*) followed by radical cystectomy is associated with improved survival in patients with locally advanced bladder cancer (pT2-pT4).

~40% of patients have a complete pathologic response (ypT0). Patients with a complete response do significantly better than those with residual disease (85% are alive at 5 years). Grossman et al. NEJM. 349: 859-866, August 2003.

\*M-VAC: methotrexate, vinblastine, doxorubicin (adriamycin), and cisplatin



#### Other Bladder Tumors

Urothelial carcinoma accounts for 90% of bladder tumors; however, other tumors do occur.

-Squamous cell carcinoma

Only call it squamous cell carcinoma if there is no conventional urothelial carcinoma present; rare tumor, higher incidence in areas with schistosomiasis.

- Small Cell Carcinoma
- Clear Cell Adenocarcinoma
- Metastatic Tumors
- Sarcomas: such as rhabdomyosarcoma

#### Adenocarcinoma

By definition the tumor is comprised entirely of glandular elements. Primary pure adenocarcinomas are rare (2.5% of bladder malignancies).

Split into urachal carcinoma and non-urachal. Non-urachal adenocarcinomas are associated with a worse prognosis.

Different histologic types: NOS (non-descript glands), enteric (colonic) type, mucinous (colloid), clear cell.

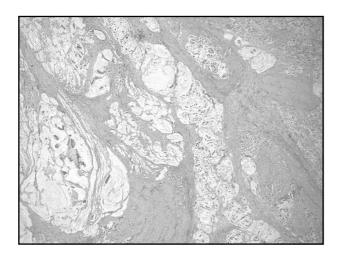
Must consider metastases in the differential diagnosis.

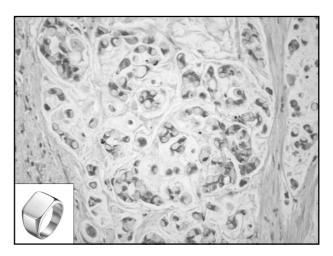
#### Urachal carcinoma

Defined as primary carcinoma derived from urachal remnants.

For a tumor to be considered urachal it should be localized to an area near or at the dome, the overlying bladder epithelium may be ulcerated but no in situ carcinoma, and glandular metaplasia is absent

Most often they are mucinous (colloid), but can also be enteric, signet ring cell or mixed.





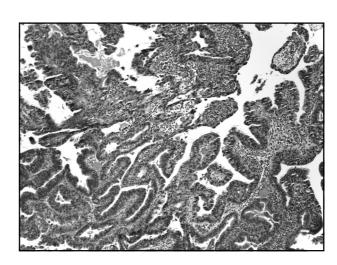
## Primary vs Metastasis

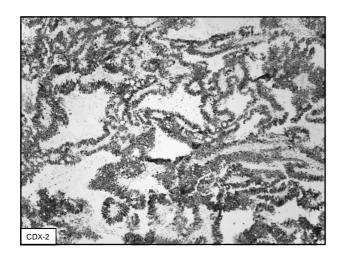
Often immunohistochemistry is not too helpful. Typical urothelial carcinomas are CK7 positive (90%), CK20 positive (65%), p63 positive (85%), 34BE12 positive (65%), GATA3 (75%).

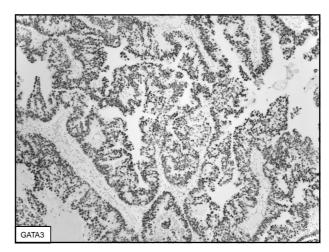
Adenocarcinomas of the bladder often lose p63 and 34BE12 expression and CK7 may be reduced.

GATA3 positive in up to half of cases.

CDX-2 (positive in gastrointestinal tumors) can be positive (and can be diffuse and strong).





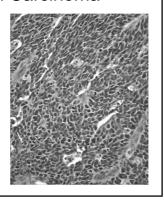


### Small Cell Carcinoma

Characterized by an aggressive clinical course. Important to make the diagnosis since it will influence chemotherapy.

Histologically characterized by cells with high N:C ratio, with nuclear molding, numerous mitoses, and apoptotic cells.

Can use stains such as synaptophysin and chromogranin – markers of neuroendocrine differentiation to confirm histologic impression.





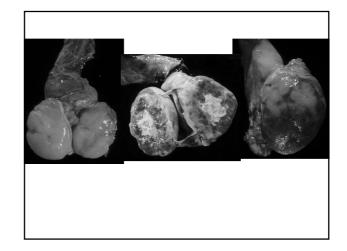
## **Testicular Tumors**

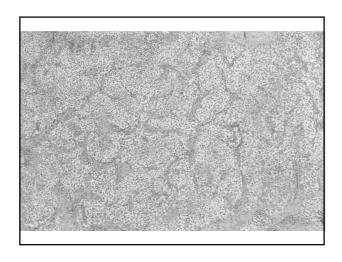
## Dr R.H. Young

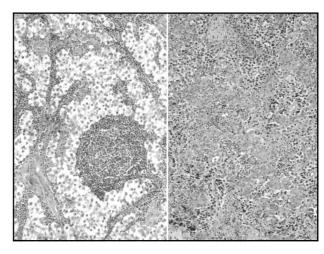
## Disclosure Statement

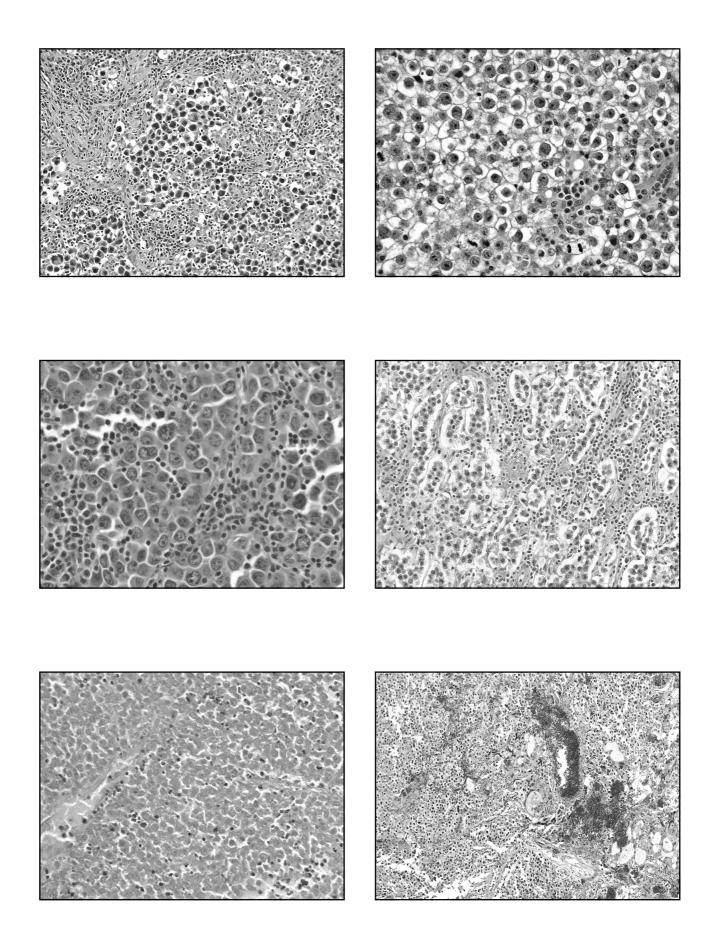
• Nothing to disclose

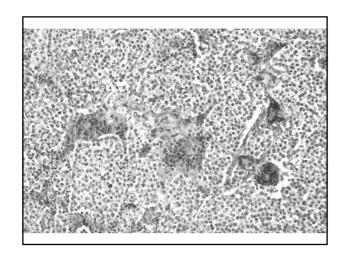
(	Germ Cell 7	<b>Tumors</b>	
Pure	67%		
Semino	ma	53%	
Typical			52%
Spermatocytic			1%
Embryonal ca			10%
Teratoma		3%	
Yolk sac tumor		0.4%	
Polyembryoma		0.3%	
Choriocarcinoma		0.3%	
Mixed	33%		

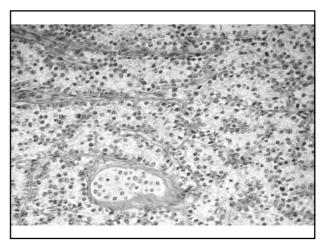


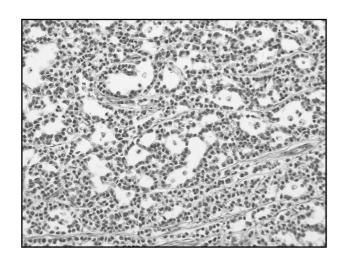


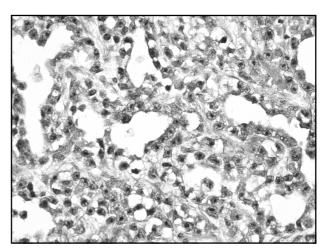


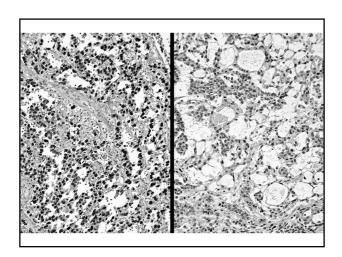










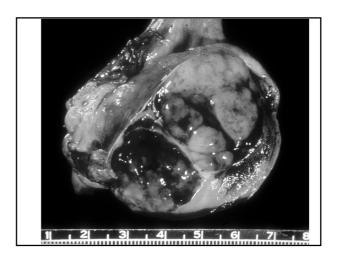


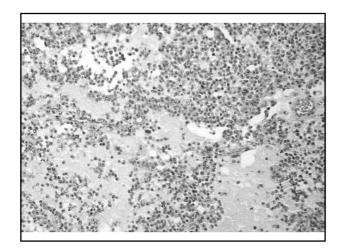
## SEMINOMA – DIFFERENTIAL DIAGNOSIS

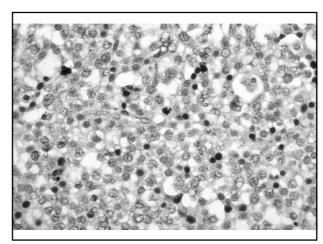
- 1. Spermatocytic seminoma
- 2. Embryonal carcinoma
- 3. Choriocarcinoma
- 4. Solid yolk sac tumor
- 5. Lymphoma
- 6. Sertoli cell tumor

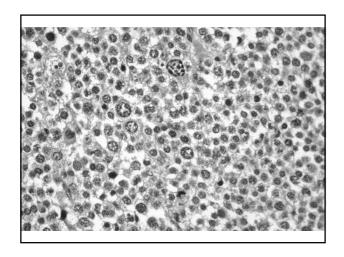
# SPERMATOCYTIC SEMINOMA

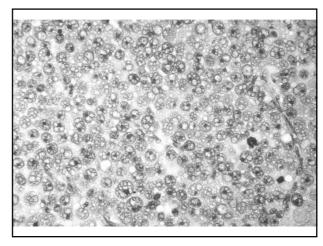
- **1. Pierre Masson 1946**
- 2. **Robert E. Scully 1961**
- 3. Juan Rosai 1969





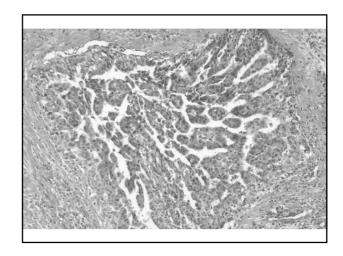


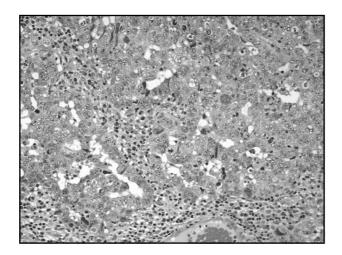


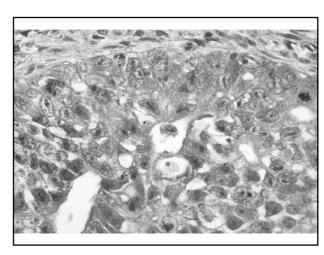


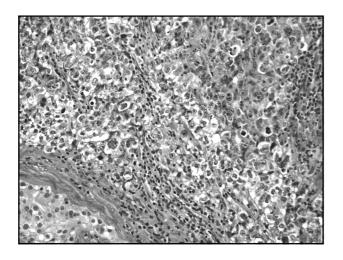
## Spermatocytic Seminoma

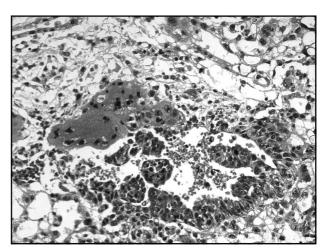
Always pure No lymphocytes No Granulomas No Glycogen Unequal, Round Nuclei Sarcomatous Change

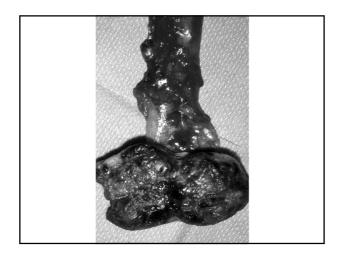


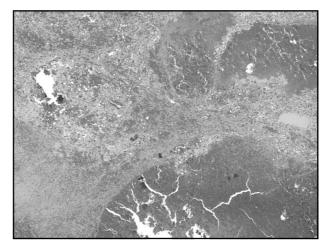


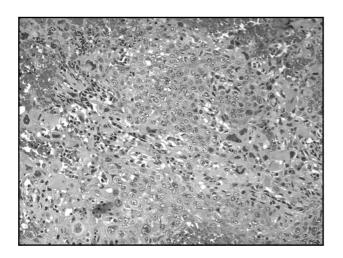


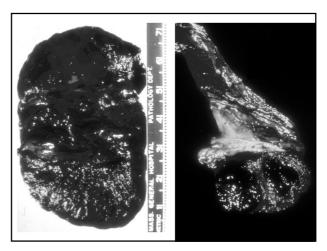


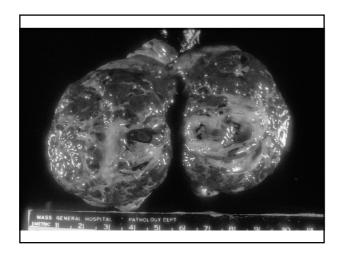




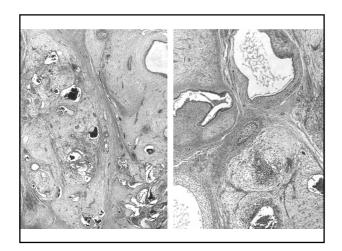


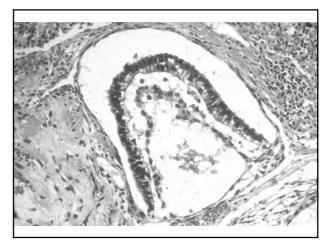


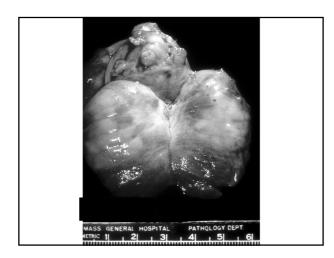


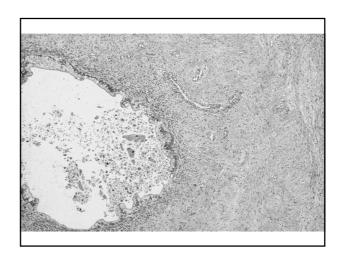


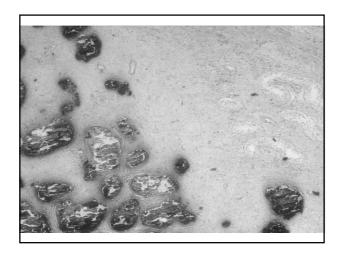


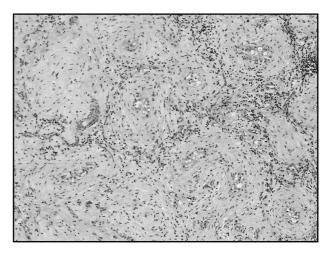


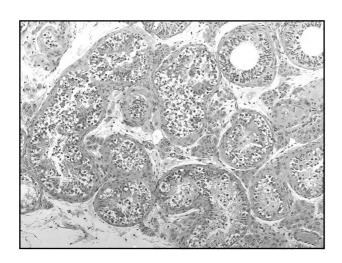








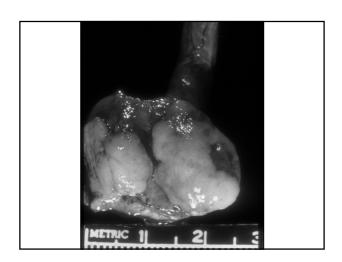


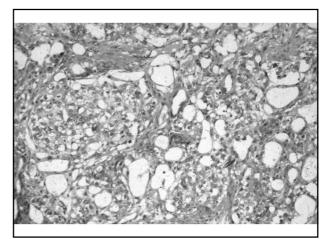


## TESTICULAR TUMORS IN CHILDREN

Teratomas 48%
Yolk sac tumor 15%
Epidermoid cyst 14%
Sex cord tumors 13%
Miscellaneous 10%

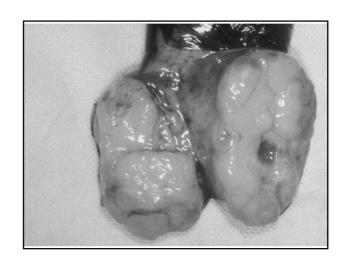
Pohl et al. J Urol 172:2370, 2004

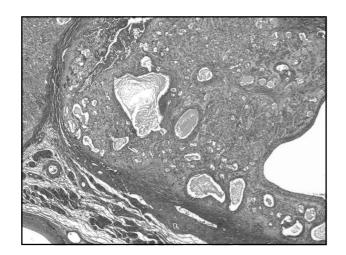


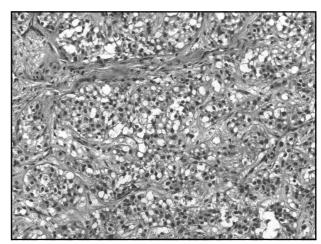


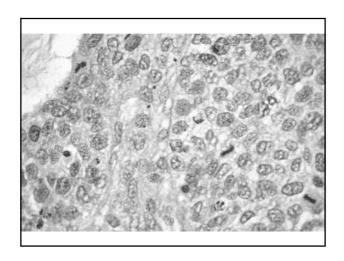
### **Sex Cord-Stromal Tumors**

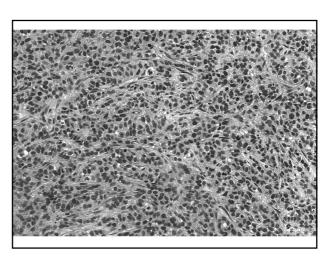
Leydig cell tumors Sertoli cell tumors Sertoli-Leydig cell tumors Granulosa cell tumors, adult and juvenile Mixed and unclassified tumors

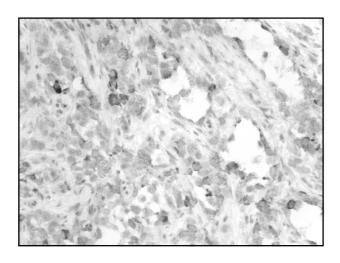


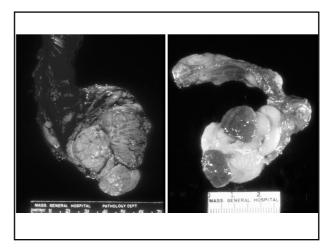


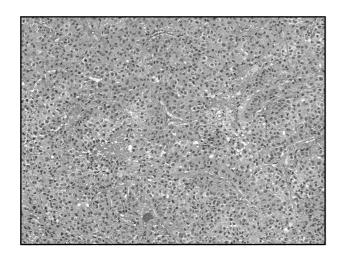


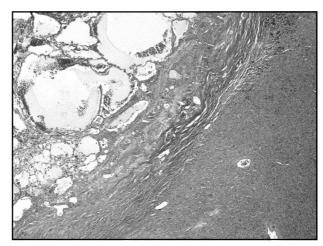


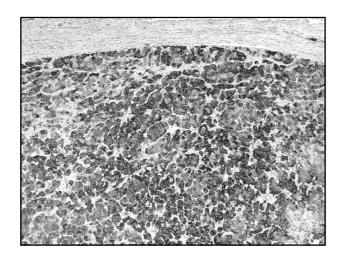


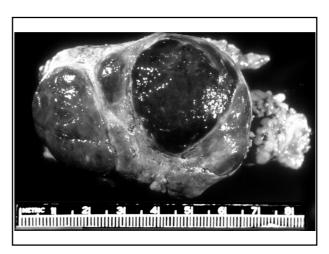


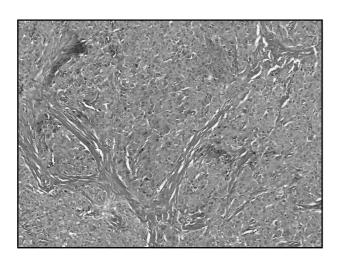


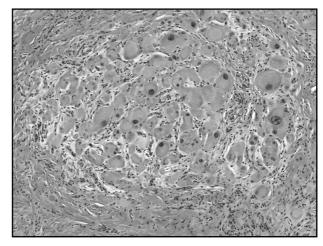






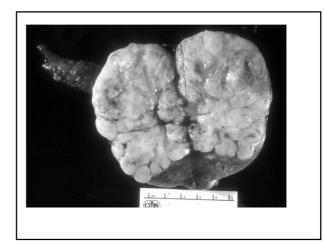


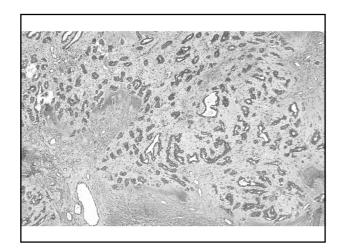


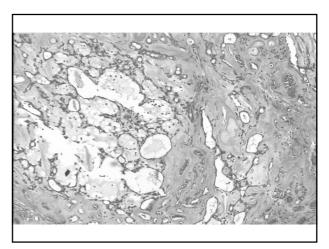


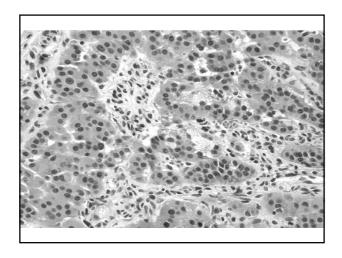
## TESTICULAR SERTOLI CELL TUMORS

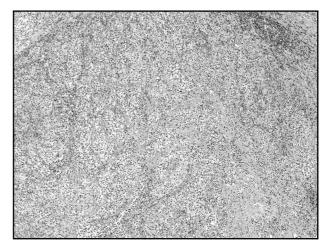
- Sertoli cell tumor, not otherwise specified
- Large cell calcifying
- Sclerosing
- Tumors in Peutz-Jeghers syndrome

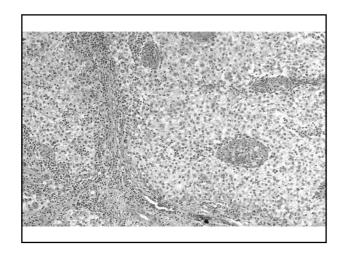


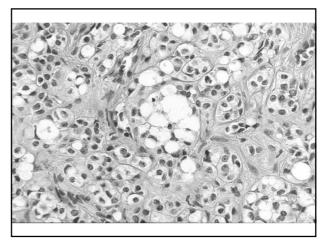


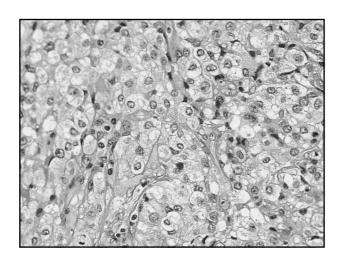


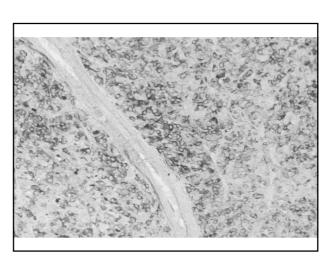


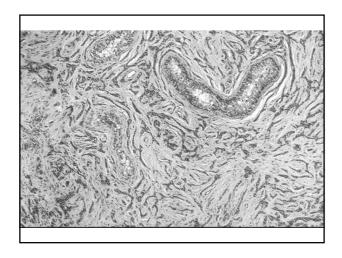


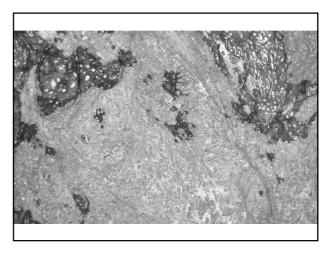






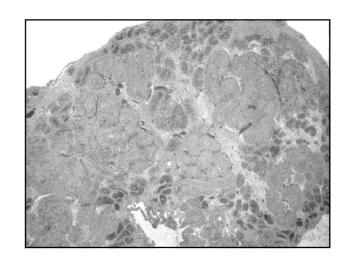


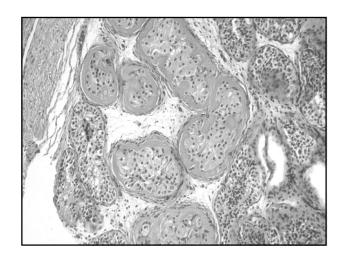


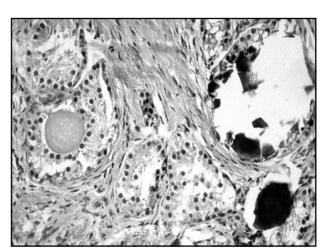


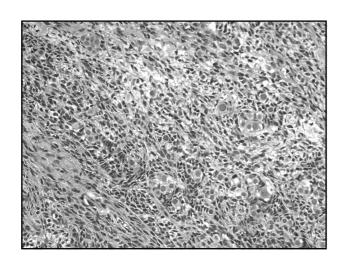
## LCCST VS. SCT, NOS

Bilateral40%CA++100%Intratubular50%Large cells, abundant cyto100%



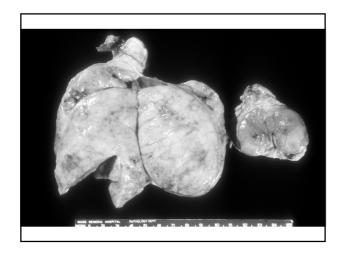


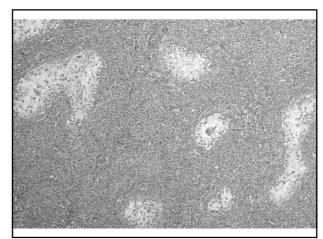


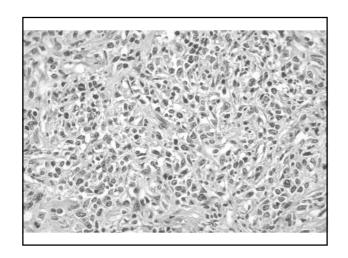


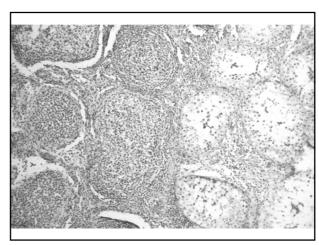
## Testicular Tumors in the 50 + Age Group

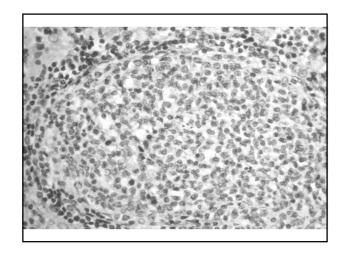
- Lymphoma
- Metastases
- Spermatocytic Seminoma











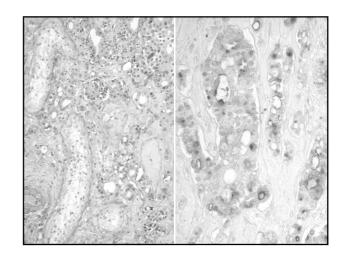
## Mets To Testis

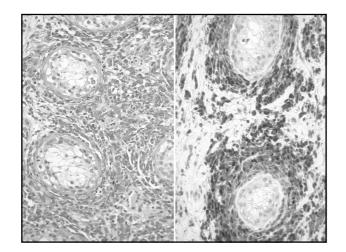
Symptomatic 15%

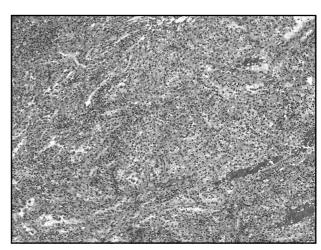
Presenting Symptom 4%

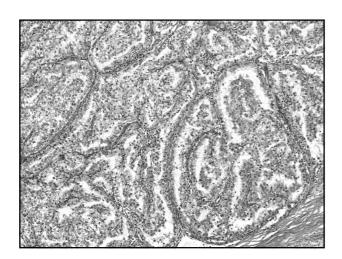
## Mets To Testis

• Prostate	43%
• Lung	15%
• Colon	10%
• Kidney	10%
• Stomach	7%
• Melanoma	4%
• Misc.	11%



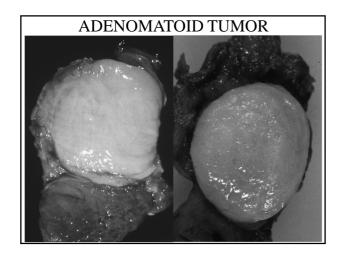




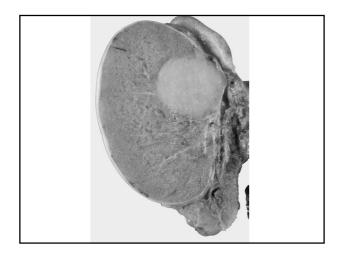


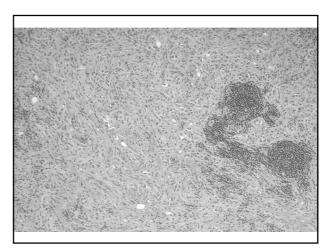
## **Paratesticular Tumors**

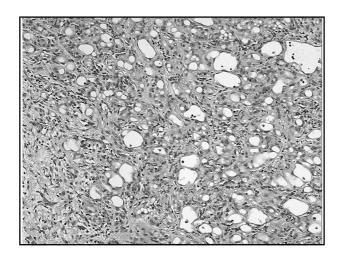
Sertoliform rete
cystadenoma
Rete carcinoma
Adenomatoid tumor
Malignant mesothelioma
Mullerian carcinomas

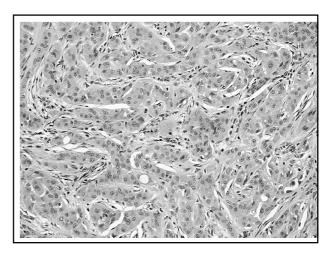


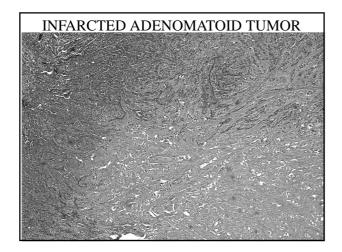








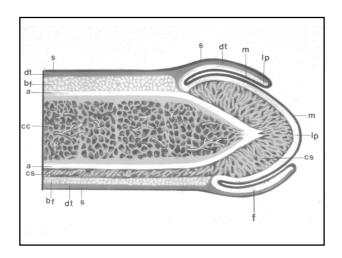


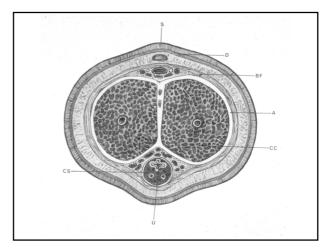


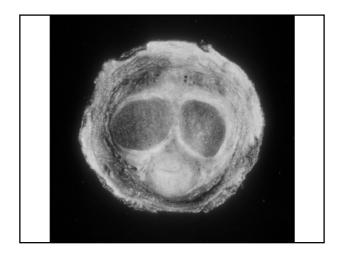
## Pathology of the Penis Dr R H Young

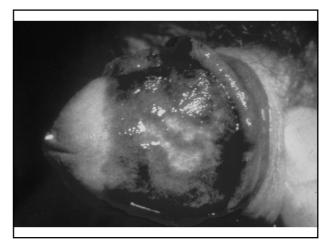
## Disclosure Statement

• Nothing to disclose

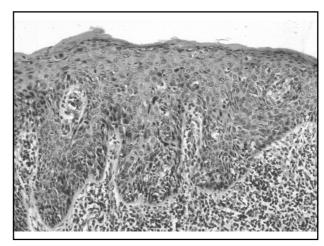




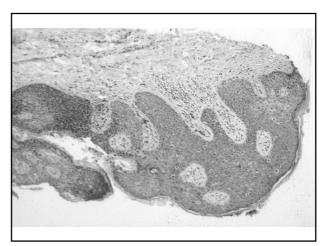


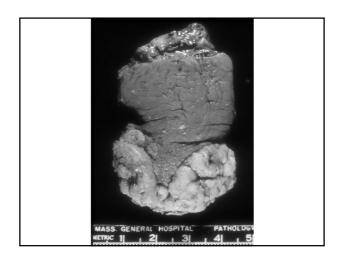


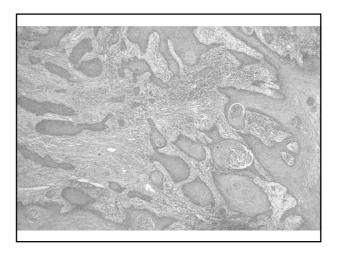


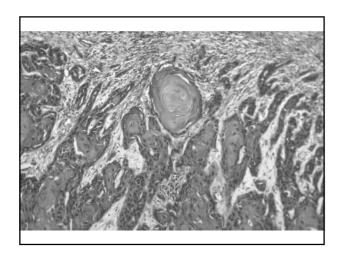


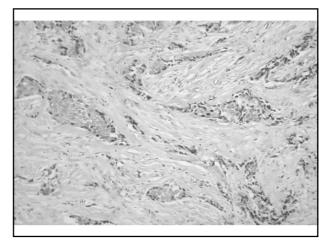


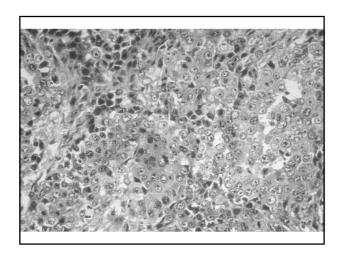


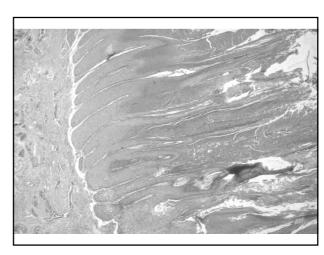


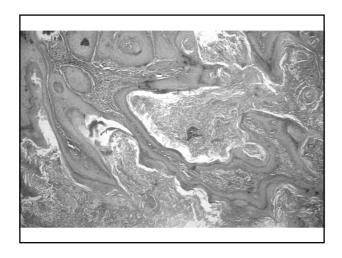


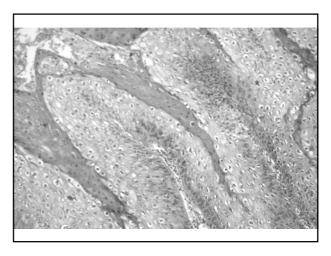


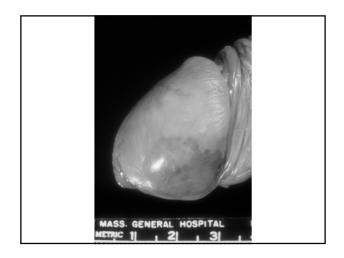


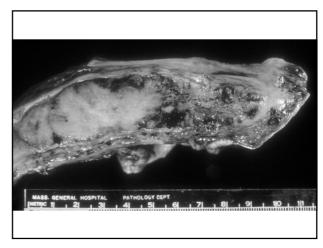








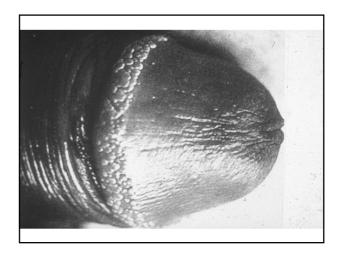


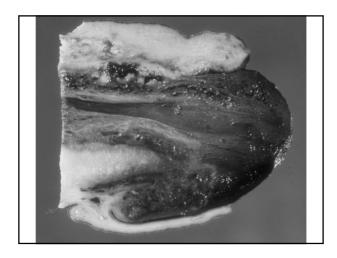


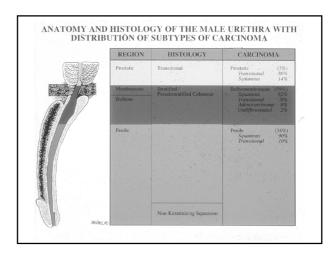


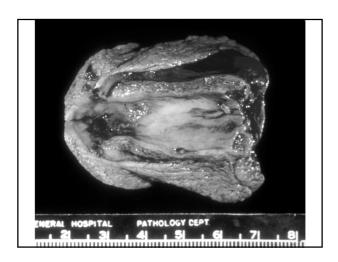




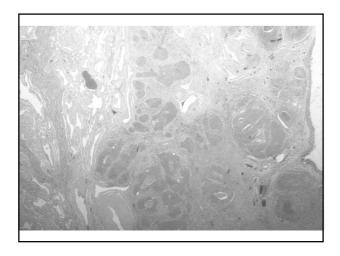


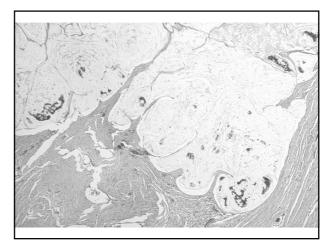




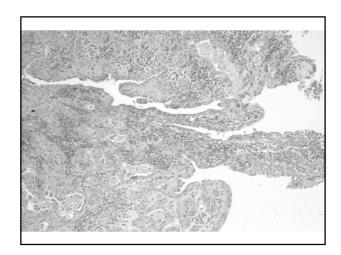


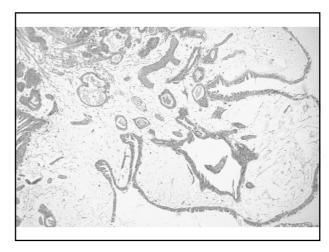


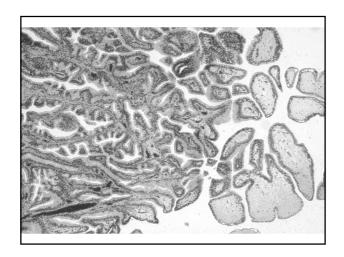


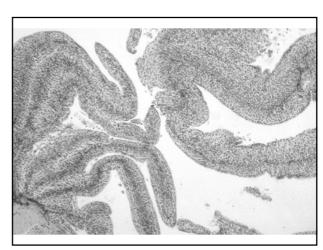


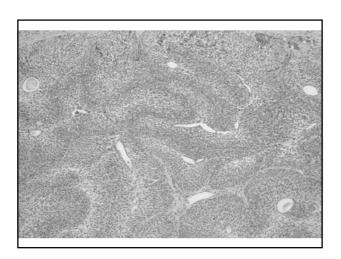
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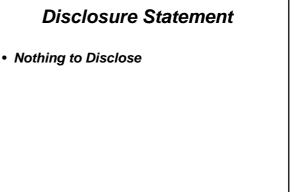
## Jay Simhan, MD, FACS

Vice Chair, Department of Urology, Einstein Medical Center Associate Professor of Urology, Fox Chase Cancer Center

Philadelphia, PA Einstein Urology

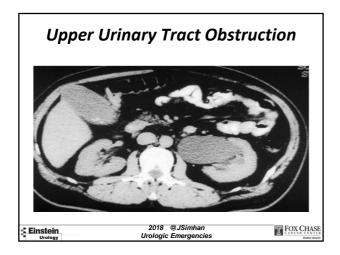
2018 @JSimhan Urologic Emergencies FOX CHASE

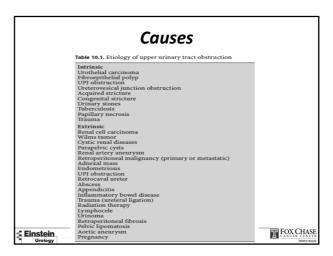
Einstein



2018 @JSimhan

FOX CHASE





## **Presentation**

- Flank pain, LQ pain +/- fever
- Decreased UOP (usually only in bilateral, dehydration or CKD)
- LUTS (with distal stones)

2018 @JSimhan Urologic Emergencies FOX CHASE Einstein

## Workup

- CT renal colic
- KUB if stones present prior to d/c (ESWL v
- UA/Urine Culture (Every Patient)
- CBC,BMP
- Vital Signs

2018 @JSimhan Urologic Emergencies FOX CHASE Einstein

## **Treatment**

- Emergent Stent or PCN
  - Hydronephrosis and fever>38.0
  - Hydronephrosis and bacteriuria (cath specimen in women)
  - Hydronephrosis +SIRS symptoms (hypotension, tachy>120, ect.) PCN for unstable patients
  - Bilateral stones with bilateral Hydronephrosis
  - Solitary kidney with Hydronephrosis

Einstein 2018 @JSimhan FOX CHASI
Urology Urologic Emergencies

## **Treatment**

- Other patients that may require sub-acute treatment (usually admission and treat w/in 1 week)
  - Hydronephrosis and decreased GFR
  - Poor pain control/intractable nausea/vomiting
  - High grade obstruction >4 weeks.

Einstein 2018 @JSimhan FOX CHASE

## **Treatment**

- Non-infected obstructing stones w normal contralateral kidney
  - Doxazosin/flomax, urinary strainer
  - May give toradol if Cr w/n/l
  - Get KUB and CT renal colic in ED
  - F/U with outpatient urologist
  - Send urine culture , do not treat with Abx

Einstein 2018 @JSimhan Urologic Emergencies FOX CHASE Description of the Urology Urologic Emergencies

## **Treatment**

- Non-obstructing stones (No Hydronephrosis)
  - Referral to outpatient urologist
  - Treat UTI with PO abx if present
  - Get CT and KUB in ED prior to D/C

Einstein 2018 @JSimhan
Urologic Emergencies

## Case Examples

- 32 Female with 8mm stone in the lower pole R kidney. No HN on CT scan.
- UA c/w UTI
- No Fevers, +flank pain
- WBC 14, Cr 0.6

Einstein 2018 @JSimhan Urologic Emergencies Institute In

## Answer

- UTI/Nonobstructing stone
- Get KUB to evaluate for ESWL candidate
- Treat UTI empirically
- Send Ucx.
- Urology referral for next available appointment

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## Case Example

- 52 diabetic male with flank pain and fevers to 101F at home, N/V.
- CT with 6mm proximal ureteral stone with UA with 25WBC, nitrite +
- WBC 18, Cr 0.8, Gluc 300
- BP 120/80, HR 90

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Urology Urologic Emergencies

### Answer

- Infected/Obstructed Stone
- Urologic consultation
- IV Abx (Vanc/zosyn or Amp/Gent)
- Glucose control
- IVF
- Urgent/Emergent decompression

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## Case Example

- 42F with L flank pain and fever to 103, lethargy, chills.
- CT scan with 4mm distal ureteral stone with mild/moderate HN.
- BP 83/40, HR 125 in ED

Einstein
Urology
Urologic Emergencies

### **Answer**

- Infected/obstructing stone with patient with hypotension/tachycardia >120.
- Emergent urology consultation, IV Abx, IV fluids
- Will get emergent PCN placement by IR and will need admission to ICU.

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## Case Example

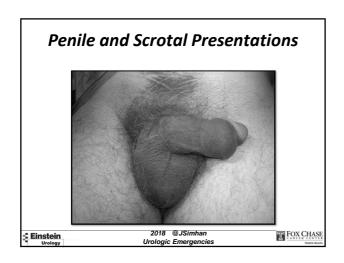
- 32 male with flank pain/N/V x 3 days
- CT with 8mm proximal right ureteral stone with moderate/severe HN
- UA with 6wbc, nitrite -, 20rbc
- BP 125/77, HR 65
- WBC 16, Cr 1.0
- No fever

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Urologic Emergencies

## **Answer**

- Non-infected obstructing stone
- If pain controlled in ED and tolerating PO
- KUB prior to d/c, Ucx
- Urologic phone consultation for surgical planning (ESWL v URS w/in 1 month)
- Referral to outpatient urologist w/in 2 weeks.

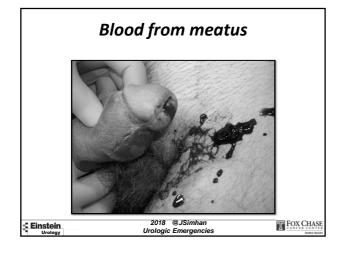
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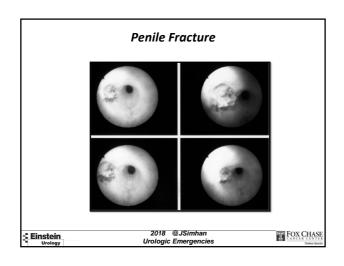
## Penile Fracture

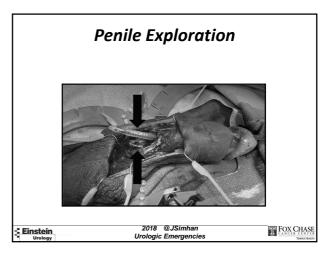
- "I heard a pop during sexual intercourse"
- Patient usually looses erection immediately
- "Eggplant deformity"
- May have hematuria if urethral injury as well
- Needs Urological consultation and penile exploration to avoid permanent ED.

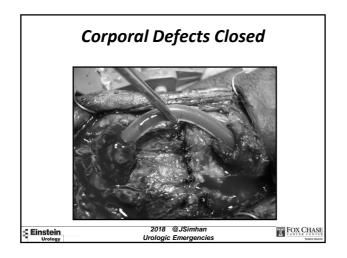
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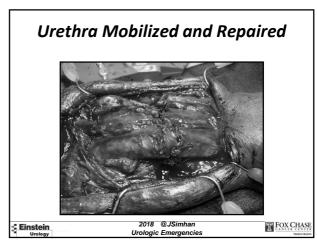


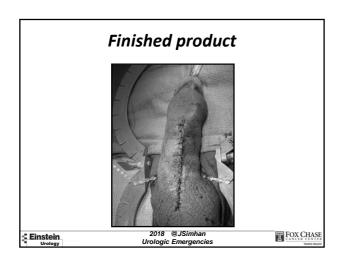


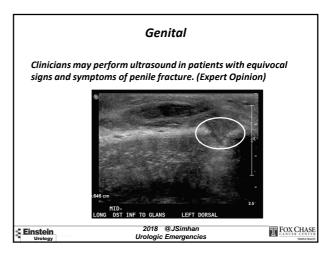




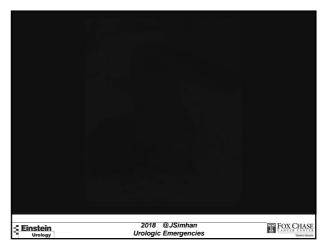


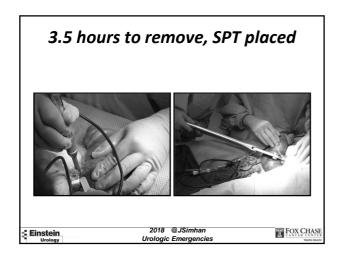


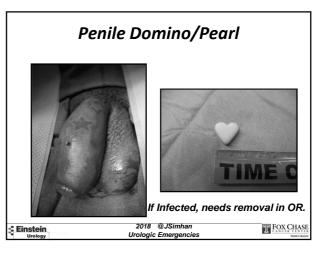


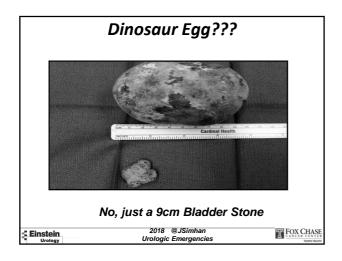


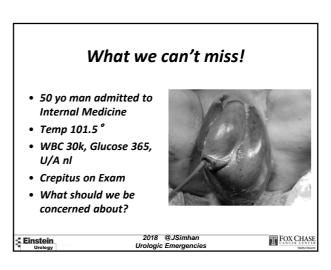














## Fournier's Gangrene

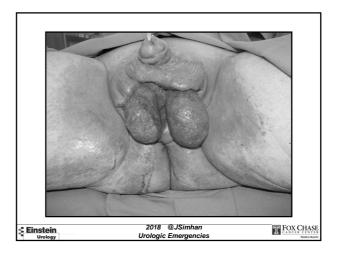
- Necrotizing Fasciitis of the scrotum, perineum, penis, ect.
- Surgical emergency
- If Crepitus, no need for imaging, straight to
- May get CT scan or U/S if borderline presentation and no crepitus.
- Tight glucose control, IV Abx, IVF
- Mortality historically 25% (???)

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## Fournier's Gangrene

- Many times urologic and general surgery consulation needed. If only scrotal/penile ->urology.
- If only perianal/perineal, no scrotal involvement ->EGS

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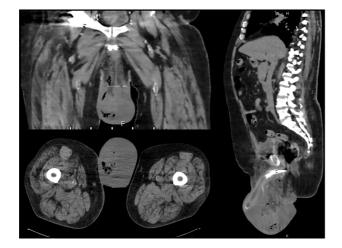
## Case Presentation

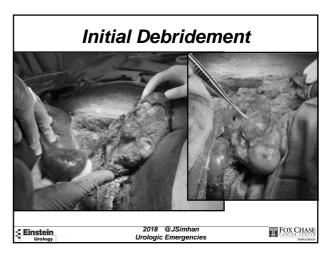
- 75M diabetic with a h/o Prostate ca s/p prostatectomy (2003) and inflatable penile prosthesis (IPP, 2003)
- Presents to the ER with scrotal pain, fevers.
- T 38 HR 120 RR 20 BP 123/61 98% RA
- Physical Exam: severe penoscrotal swelling with foul smelling drainage from the perineum
- Wound Cx: Enterococcus, Bacteroides, Blood Cxs: neg

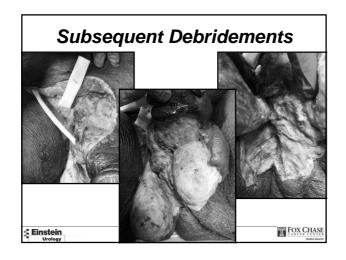
10.3 174 132 98 3.3 275

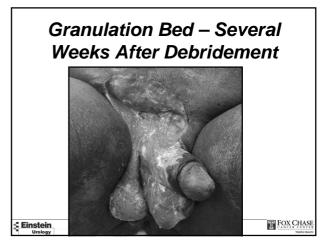
10.3 174 4.8 22 3.9 275

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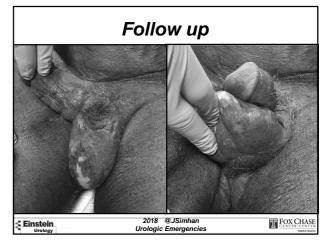


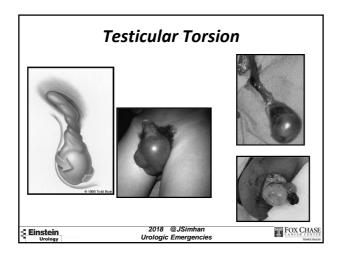












## Testicular Torsion • More common in boys age 12-16, but can happen at any age. • Usual presentation is severe scrotal pain with radiation into abdomen associated with N/V. • May have high-riding testicle with obvious twisting. • Time critical ischemia-8hr window to save the testicle. Einstein 2018 © JSimhan Urologic Emergencies

## **Testicular Torsion**

- If story is classic, no need for imaging.
- Urologist needs to be consulted immediately
- If UA positive, consider epididymitis and get U/S.
- Even if manually detorsed (open book), still needs urgent surgery.
- Surgical treatment is scrotal expl, detorsion w orchiopexy v orchiectomy, pex other side.

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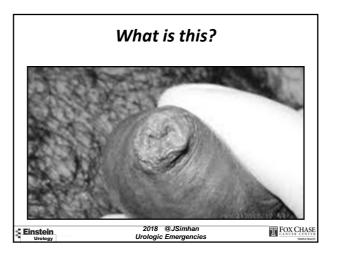
Urologic Emergencies



## **Testis Mass**

- If concern for testis mass, should get tumor markers (AFP, HCG, LDH), and scrotal U/S.
- Typically recommend admitting patients for an inpatient orchiectomy, staging CT scans ASAP as to not risk losing the patient to f/u.

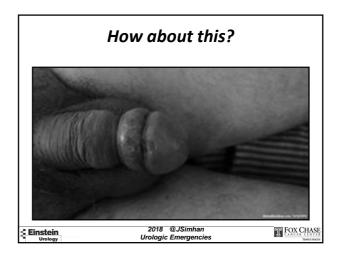
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## **Phimosis**

- Scarring of the uncircumcised foreskin with inability to retract.
- Treatment is circumcision or dorsal slit procedure.
- Would not force retraction for fear of paraphimosis
- If infected (balanitis), may clean with qtip with bacitracin, antifungal. Rarely requires oral Abx.

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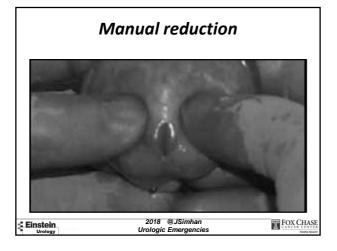




## **Paraphimosis**

- A condition where the foreskin gets trapped behind the glans penis.
- Eventually with increased edema, can get ischemia and necrosis of the glans
- Treatment is manual retraction
- If unable to manually retract, urgent urologic consultation is required

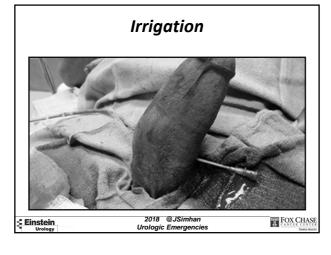
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Urology	Urologic Emergencies	TIMPU HOUSE

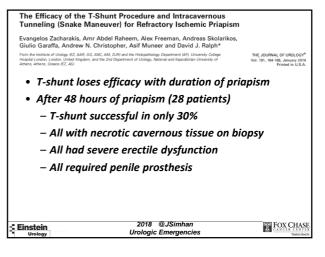


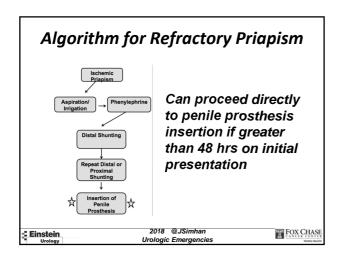
## Ischemic Priapism

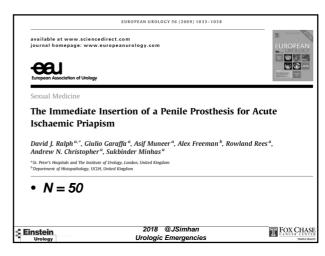
- Prolonged painful erection >4hours.
- Causes- sickle cell, ED medications, meds
- >48 hours increase risk of permanent ED
- Terbutaline (Efficacy unknown)
- Tx irrigation and phenylephrine injection, must be in booth with HD monitoring
- If fails, multiple shunt procedures may be successful
- If shunts fail or >48 hrs, place penile prosthesis

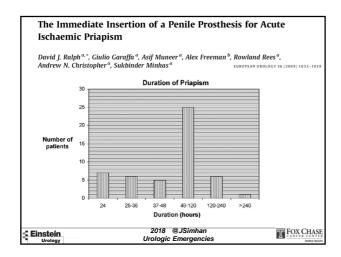
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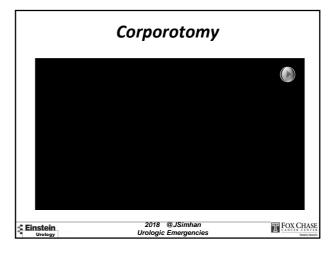


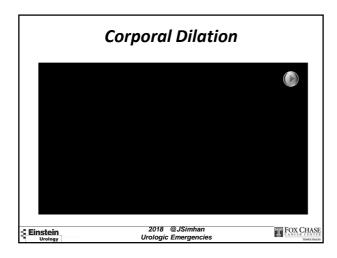


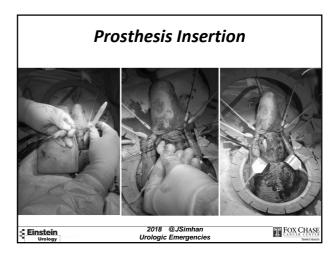








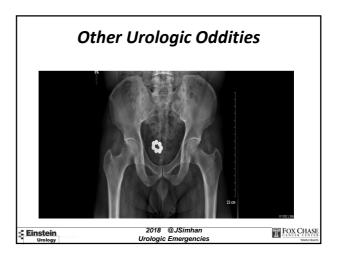




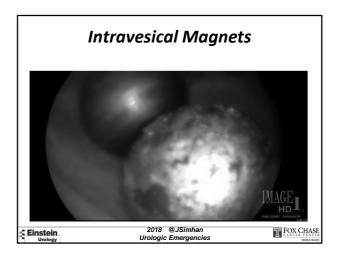
## Take Home Messages

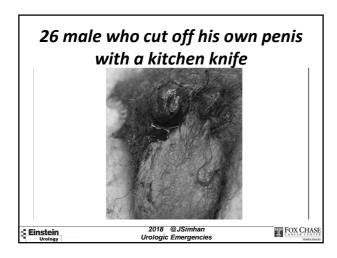
- Management of refractory priapism is associated with multiple ED visits and hospital admissions.
- Penile prosthesis is efficacious in treating refractory priapism durably with cost and resource benefits

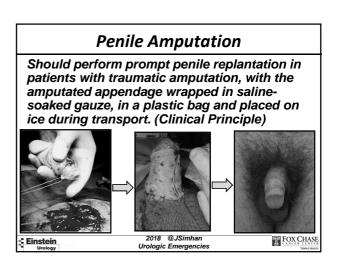
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# Foreign Body in the Bladder Linstein Urologic Emergencies Foreign Body in the Bladder







## "Two bag system"

- Rinse with saline, wrap in gauze and moisten with saline
- Place in biohazard bag



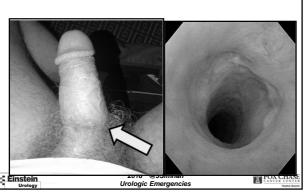
• Place bag in a saline/ice slush for transport

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## s/p Penile Replantation



## **Urinary Retention**

- Difficulty with urination often requires Foley catheter.
- Most common reasons are urethral stricture disease or BPH

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## **Coude Catheter**

- Ideal for BPH, difficulty at level of prostate
- Balloon port follows curvature
- Tip up at 12 'Oclock
- "Bigger is better" (18/20F)

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## **Urethral Stricture**





Reconstructive Urology

**Urethral Rest: Role and Rationale in Preparation for Anterior Urethroplasty** 

Ryan P. Terlecki, Matthew C. Steele, Celeste Valadez, and Allen F. Morey

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## Reconstructive Urology

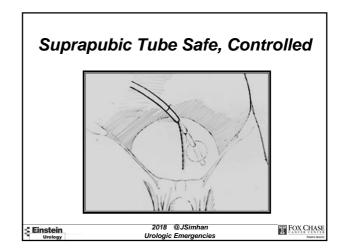
## Urethral Rest: Role and Rationale in Preparation for Anterior Urethroplasty

Ryan P. Terlecki, Matthew C. Steele, Celeste Valadez, and Allen F. Morey

- Frequently referred with:
  - ✓ Indwelling urethral catheter (remove)
  - ✓ Active regimen of self-catheterization (stop)
  - ✓ Recent dilation/endoscopic interventions (wait) Urology 2011

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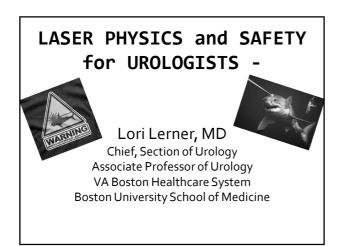


## **Conclusions**

- Infected/obstructed stones require urgent drainage
- Every ER stone patient needs a urine culture
- Do not forget the GU exam and make sure foreskin is retracted after foley placements, other manipulations.
- Keep your eye out for the time-critical dxs (torsion, Fournier's, priapism, paraphimosis)

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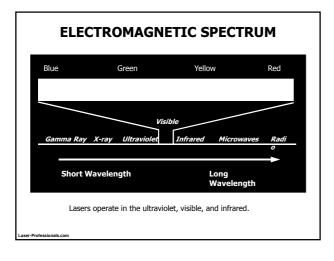


## Disclosures

 Consultant and Preceptor for Boston Scientific and Lumenis

What is the goal of most energy sources we use in surgery? What are we trying to do?

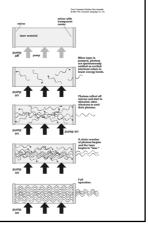
Light
Amplification
by Stimulated
Emission of
Radiation

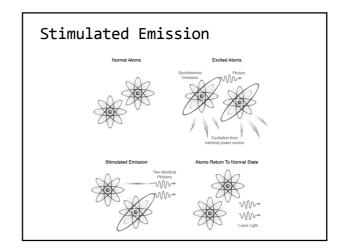


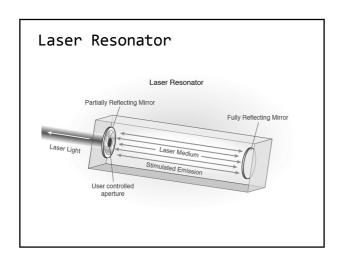
## Stimulated Emission

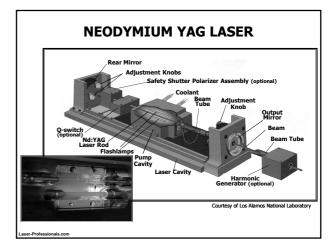
- Outermost electrons of atoms in resting state
- External energy (electricity) raises electron to a higher state
- Emitted photon strikes another atom already at higher state
- As atom returns to resting state it emits photon of energy and wavelength characteristic of the emitting atom
- First photon continues on and second atom releases an additional photon with the same properties of the first

- Emission occurs in active medium of the laser which is contained within the laser resonator
- Active medium can be solid, gas, liquid, or semiconductor
- Laser resonator contains two parallel mirrors, one allows transmission of light and another reflects the atoms back into the resonator causing continued stimulated emission and buildup of energy



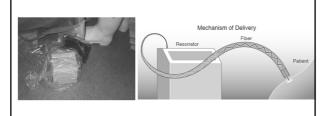






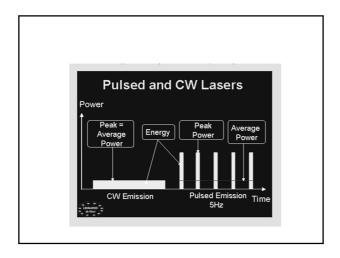
## Energy Delivery

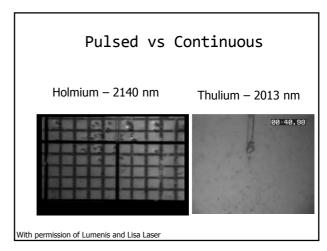
- Energy stored and released in a pulsed or continuous fashion, controlled by a foot pedal or switch
- Energy travels along the laser fiber through internal reflection that "bounces" the energy down the fiber



## Duration of Laser Emission

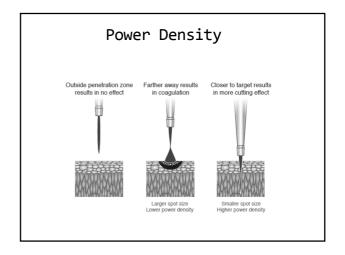
- CONTINUOUS WAVE lasers operate with a stable average beam power. In most higher power systems, one is able to adjust the power.
- PULSED (normal mode) lasers can be characterized by a set of parameters such as pulse energy, peak power, duration, mean optical frequency and arrival time. Durations are generally few hundred microseconds to a few milliseconds.
- Q-SWITCHED laser is a pulsed laser which contains a shutter-like device that does not allow emission of laser light until opened. Energy is built-up in a Q-Switched laser and released by opening the device to produce a single, intense laser pulse.



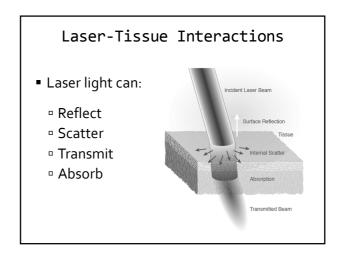


## Laser characteristics

- Energy
  - Expressed in Joules
- Frequency
  - Expressed in Hertz
- Power
  - Rate at which energy is delivered
  - Expressed in Watts
  - Joules x Hertz = Watts
- Power Density
  - Watts per centimeter squared (at target surface)



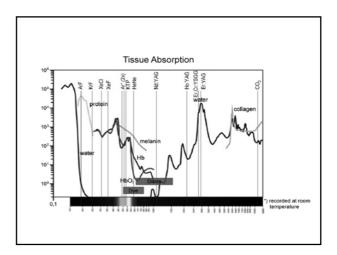
## Nondivergent/collimated (always in parallel) Monochromatic (same wavelength) Coherent (waves travel in phase)

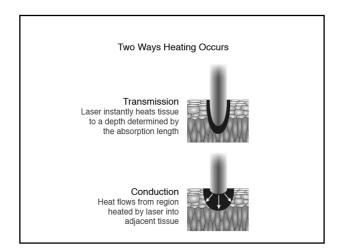


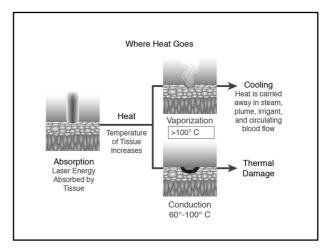
## Laser-Tissue Interactions

- Absorbed photons raise temperature and destroy cells
- Depth of penetration is distance in which 90% of laser energy deposited
- Wavelength of laser photons affects tissue interactions
- Tissue has different absorption coefficient for each wavelength
- Important characteristics include hemoglobin, pigmentation content and chemical composition

Temp Threshold	Biological Effect
37 °C	Body temperature
45 °C	Hyperthermia
60 °C	Coagulation (near tissue)
100 °C	Vaporization / Cutting (contact with tissue)
150 °C	Carbonization
300 °C	Melting



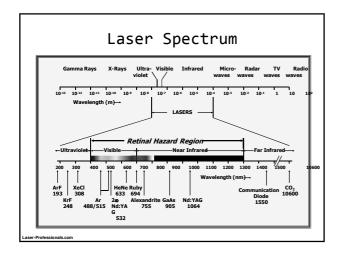


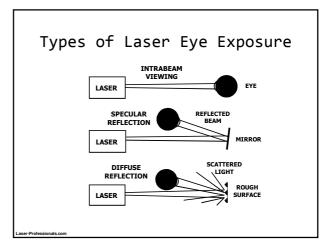


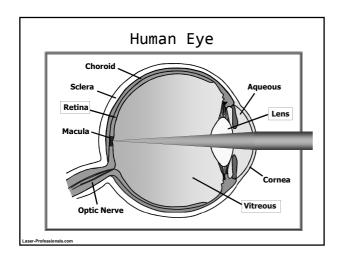
## Fiber Thermal Confinement • Time in one spot • Power level • Temperature • Tissue composition • Irrigation cooling • Sweep Speed Courtesy of Dr. Alex Te

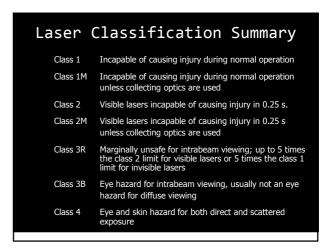
## Laser Safety

- It is imperative that lasers are used safely for the patient, surgeon, and operating room personnel.
- Given the different characteristics, different lasers have different safety concerns.
- The most common injuries associated with lasers are skin burns and eye injury, including permanent vision loss.

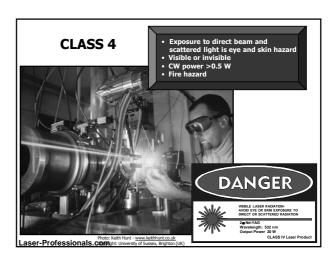


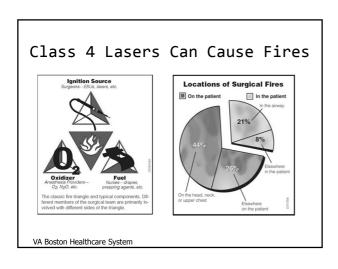








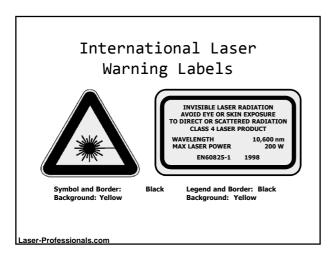




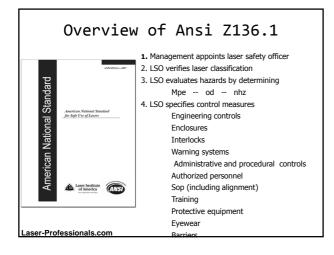
## Laser Safety Standards

- The Federal Laser Product Performance Standard (FLPPS) of the Center for Devices and Radiological Health (CDRH).
   This is federal law and applies to the <u>manufacturer</u> of lasers.
- The American National Standard for Safe Use of Lasers (ANSI Z136.1) This is a <u>VOLUNTARY</u> Standard that applies to the <u>use</u> of lasers. It is recognized by The Occupational Safety and Health Administration (OSHA)
- IEC 60825 International Standard

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## Open Beam Control Measures Ansi Section 4.3.1.1 Laser Controlled Area Eye Protection Beam Control Administrative and Procedural Controls Education and Training

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## Laser Safety Eyewear



## Securing the laser fiber -Laserdock

- Single use, disposable
- Accommodates fibers up to 2.3 mm in diameter
- Attach to drape with snaps





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## Securing the laser fiber





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## Safe Work Practices

- Operate class 3B and 4 lasers only in an area designed for laser operation and be certain that the beam is terminated on a diffuse beam block at the end of its use path.
- Do not enter a designated Class 3B or Class 4 laser controlled area (posted with a DANGER sign) without approval from a qualified laser operator.
- Always wear laser safety eyewear if a class 3B or class 4 invisible beam is accessible.
- Remove keys from lasers when not in use if necessary to prevent unauthorized laser operation.

ser-Professionals.co

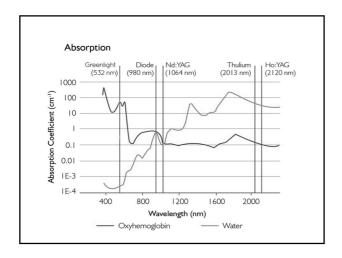
## General Standard Operating Procedure

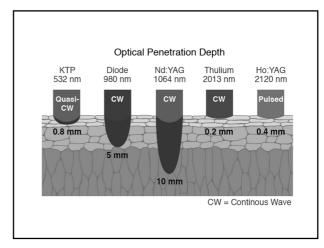
- ☼ Verify correct eyewear is available, and used as necessary.
- Uncover and/or post Laser Warning signs.
- Place at least one set of eyewear outside the NHZ.
- Turn on "Laser in Use" sign, if available.
- Close the door and cover windows, when applicable.
- Start and verify proper laser operations.
- Perform laser operations.
- When finished, turn off "Laser in Use" sign, cover/remove laser warning signs, remove keys and store keys in a secure location, if unauthorized laser use is likely.

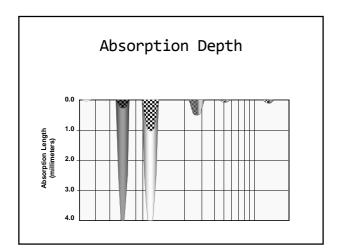
Laser-Professionals.com

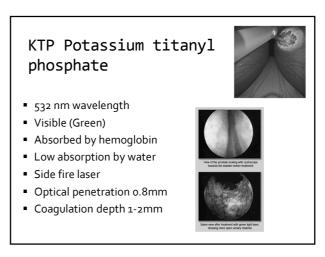
## Most commonly utilized urologic lasers

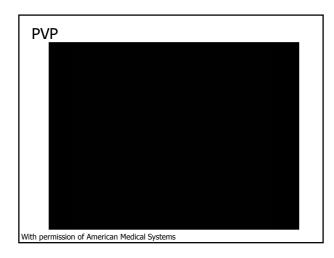
- KTP (Greenlight, PVP)
- Holmium
- Diode (Biolitec, Evolve)
- Thulium (Revolix)
- CO:
- Nd: Yag (in the past used often, making a comeback now for upper tract disease)

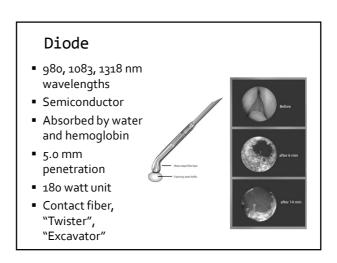


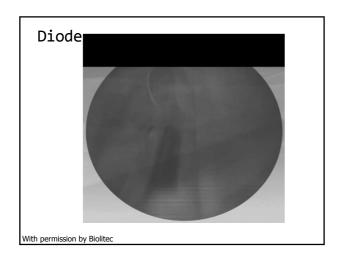








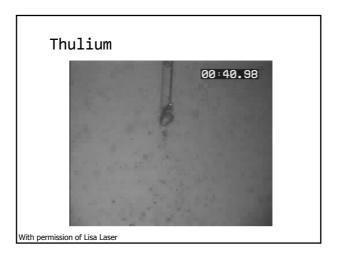




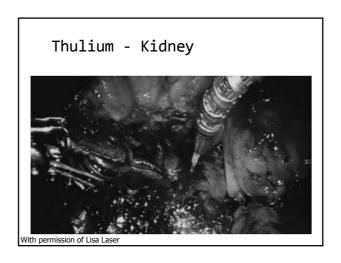


## Thulium

- Diode pumped solid state laser (DPSS)
- Absorbed by water
- 2013 nm wavelength
- Continuous energy
- o.4 mm penetration
- Revolix 50W, 70W, 120W, 200W
- Revolix Junior 15W, 30W

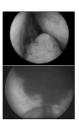






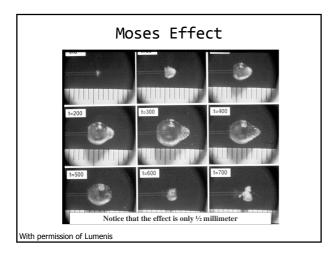
## Holmium: YAG

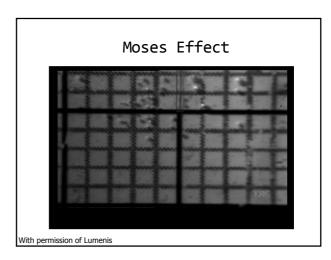
- 2140 nm wavelength
- High absorption in water
- Penetration < 0.5mm
- Energy released in a pulsed fashion
- Side or end fire fibers

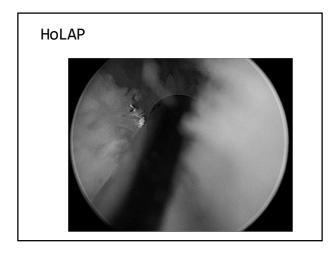


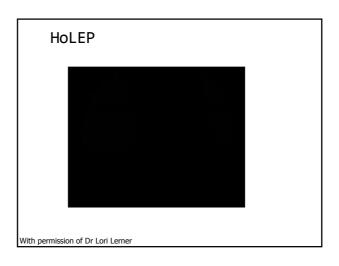
## Moses Effect

Because Holmium laser energy is well-absorbed in water, when it is released in a water-filled environment (like endourology) it actually creates a vapor bubble in the water. This is known as the "Moses Affect" since the water is parted by the bubble that forms.









## Holmium for Stones

- Turbulence comes from energy, much less from frequency
- Holmium is pulsed, so higher freq leads to less "pulse" effect
- 20 watt lasers have much less efficacy
- Dusting
  - High frequency (50-70 Hz)
  - Low energy (0.2-0.4 joules)
- Fragmentation
  - Lower frequency (10 Hz)
  - Higher energy (o.8-1.0 joules)

## Stone Dusting and Fragmenting 0.2 J and 50 Hz 3.0 J and 10 Hz With permission of Lumenis and Lisa Laser

## CO2 Lasers

- 10600 nm wavelength
- 15 and 25 watt systems
- Absorbed by water
- Very shallow penetration at 0.1 mm
- Continuous wave, pulse, and super pulse operation modes
- Depth controlled by watt level
- Coagulation range controlled by pulse duration



## CO<sub>2</sub> Lasers

- Articulating arm with end fire energy delivery
- Used for skin lesions, such as genital warts
- Now being applied to vaginal tissue
- Skin resurfacing
- Can seal blood vessels less than o.5 mm
  - Reportedly less bleeding, edema, improved post op healing





## Vaginal Rejuvenation





## Indications for Application of Vaginal Laser Therapy

- Genitourinary syndrome of menopause (vaginal atrophy associated with lack of estrogen)
- Lichen Sclerosis
- Vulvodynia/Vestibulitis
- \*\* Stress Incontinence
- \*\* Recurrent UTI's

## Available Energy Sources

- Fractional Laser Systems
  - CO<sub>2</sub> Lasers
    - Femilift Alma
    - FemTouch Lumenis
    - MonaLisaTouch DEKA/Cynosure
    - FDA approval for incision, excision, ablation, vaporization, and coagulation of soft tissue in gynecology
  - Erbium YAG Lasers
- RFA
  - Requires needles

Courtesy of Mickey Karram, MD

## Erbium YAG

- Intimalase® Fotona (not in USA)
- Incontilase ® Fotona (not in USA)
- Three treatments 30 days apart
- Strongly absorbed by water
- Has been studied for use for SUI and Genitourinary syndrome of menopause (vaginal atrophy associated with lack of estrogen)

## Vaginal Resurfacing

- Genitourinary syndrome of menopause
  - Fractional resurfacing
    - The entire surface area is not treated, reportedly improving wound healing due to existing surrounding tissue
  - Creates inflammatory reaction → fibroblasts released → new collagen formation, improved vascularity, transudate improves dryness, vagina becomes more acidic, increased lactobacilli and glycogen

## Vaginal resurfacing



https://www.youtube.com/watch?v=yP5wpoiieuU

## Conclusions

- Laser energies have properties that make them ideal tools for use in urologic surgeries and diseases
- Laser wavelengths are unique and the properties of one are not applicable to another
- Risks vary based on wavelength and it is imperative that users understand and appreciate the differences
- Above all, do no harm. Educate and inform yourself.

## Neurogenic Bladder: Recurrent Urinary Tract Infections – Beyond Antibiotics

Comprehensive Review of Urology September 21, 2018

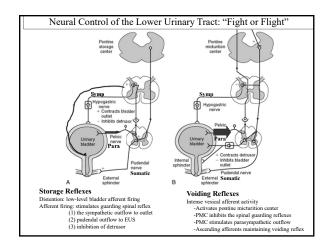
Elise J.B. De, MD Massachusetts General Hospital

## **Disclosures**

Reports no relationships with a commercial interest

## Objectives

- Approach to UTI in Neurogenic Bladder
- · Role of Emptying, Pressures, Foreign Bodies
- · Secondary workup and Intervention

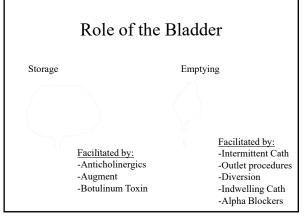


## History

- · Intake forms
- Voiding diaries
- · Active questioning:
  - Prior surgeries
  - Bowel function
  - Pelvic organ prolapse
  - Neurological disease
  - Adherence to routine health screening: PSA, Colonoscopy
  - Bladder management prior to NGB
  - Bladder management since NGB
  - Independence, Technique

## **Elevated Storage Pressures**

- Elevated bladder storage pressures from poor bladder compliance or detrusor over activity can lead to vesicoureteral reflux, impaired peristalsis of the ureters, hydronephrosis, and a theoretical risk of bacteria traversing epithelial barriers into the bladder.
  - Anticholinergics
  - Botulinum toxin
  - Continuous Drainage



## Voiding / Complete Emptying

- Voiding to completion/ emptying is a protective mechanism against UTI.
  - One animal study showing that 99.9% of bacteria injected into the bladder are eliminated by voiding
  - The higher the postvoid residual volume (PVR) the higher the risk of UTI has been found

Norden CW, Green GM, Kass EH. Antibacterial mechanisms of the urinary bladder. J Clin Invest. 1968 Dec;47(12):2689-700. Kim BR, Lim JH, Lee SA, Kim JH, Koh SE, Lee IS, Jung H, Lee J. The Relation between Postvoid Residual and Occurrence of Urinary Tract Infection after Stroke in Rehabilitation Unit. Ann Rehabil Med. 2012 Apr;36(2):248-53.

## Method of Emptying

- Patients with neurogenic bladder often require indwelling catheters or CIC
- In a retrospective study evaluating patients with neurogenic bladder, the emptying method was the most important predictor of symptomatic UTIs
- Indwelling catheterization posed the highest risk<sup>10</sup>

Krebs J, Wöllner J, Pannek J. Risk factors for symptomatic urinary tract infections in individuals with chronic neurogenic lower urinary tract dysfunction. Spinal Cord. 2016 Sep;54(9):682-6.

# PVR Ultrasound - 51798 Catheterization - 51701 Storage Emptying

## Diagnosis of UTI

- Nuanced in this population
- Impaired bladder sensation
- Do not report classic symptoms.
- Intermittent catheterization or indwelling catheters for bladder emptying
  - Associated with increased rates of bacteriuria

## **True Infections**

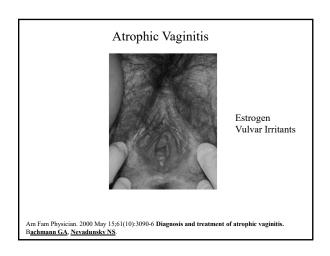
### 1st Line

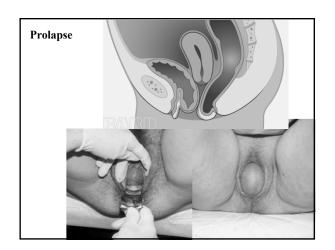
- · Upper urinary tract imaging
- Cystoscopy
- · Urodynamics/ Post-void residual
- Patients who self-catheterize: review of technique emptying
- Indwelling Cath: Management Strategy

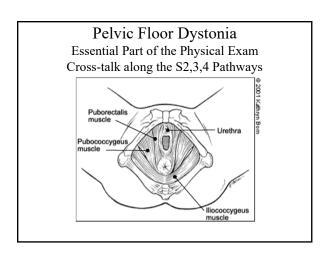
### 2nd Line

- Cystogram/VCUG: Fistula, Reflux
- · MRI: Urethral diverticulum

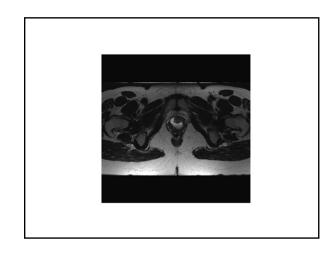
## **Coexisting Diagnoses**











#### Coexisting Diagnoses

#### Infection with Variable Cultures

- · Possible urethral irritation (Estrogen, Toilet Paper, Soap)
- · Men: expressed prostatic secretions
- · Women: vaginal swab for ureaplasma and mycoplasma
- Symptoms of UTI can derive from pelvic floor muscle spasm
   Cross sensitization along S 2,3,4 nerve pathways [Malykhina 2007]
- If "UTI" symptoms persist, workup obligatory:
  - Carcinoma in situ
  - Bladder stones
  - Urethral diverticulum

#### **Imaging**

- Renal ultrasound suffices for recurrent UTI
- Renal mass protocol CT scan or MRI should be performed instead in the case of hematuria
  - -≥ 3 red blood cells per 40x high power microscopic view on urine sediment in the absence of infection or clearly documented genitourinary trauma

#### Stones



- Urinary stasis as well as infection can cause urinary calculi
  which in turn may act as nidi for infection.
- Obstructing or large stones should be removed. Nonobstructing small upper urinary tract stones are usually thought to be benign.
- There is some evidence that removal of nonobstructing asymptomatic renal calculi in those with recurrent UTIs can resolve infections in 50%

Zanetti G, Papurella S, Trinchieri A, Prezioso D, Rocco F, Naber KG. Infections and urolithiasis: current clinical evidence in prophylaxis and antibiotic therapy. Arch lat Uvol Androl. 2008 Mar;80(1):5-12. Omar M, Abdulwahab-Ahmed A, Chaparala H, Monga M. Does Stone Removal Help Patients with Recurrent Urinary Tract Infections? J Urol. 2015 Oct;194(4):997-1001.

 $\underline{www.kidneystones.org}, \ http://urologystone.com/CH06DiagnosisOfStones/helical.html$ 

#### Constipation

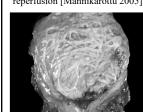
- Constipation and fecal incontinence are both thought to increase the propensity toward urinary tract infection.
- Mechanisms include perineal contamination, combined bladder and defecatory dysfunction via neural crosstalk, and trans colonic migration of bacteria.
- Intervention to address constipation or incontinence should be encouraged as part of the treatment plan for the UTI

#### Obstruction

- Renal obstruction can occur at the level of the ureteropelvic junction (UPJ), any segment of the ureter, or ureterovesicular junction (UVJ) secondary to urolithiasis, scarring, or congenital abnormalities (e.g. valves or crossing vessels).
- The bladder is often a source of obstruction due to elevated pressures, detrusor sphincter dyssynergia, pre-existing prostatic obstruction, or anterior vaginal wall prolapse.
- Obstruction anywhere in the urinary tract needs to be addressed to prevent loss of renal function, decompensation of the obstructed unit (e.g. bladder), and prevention of infection.

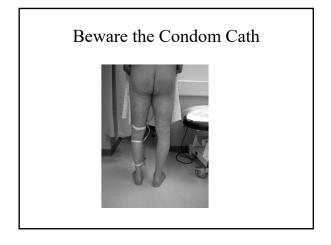
#### BOO

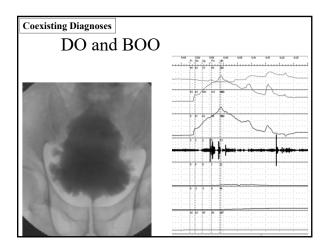
Damage to nerves, synapses and smooth muscle cells due to initial poor blood flow followed by generation of reactive oxygen and nitrogen species during reperfusion [Mannikarottu 2005].



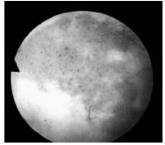


Treat BOO and OAB



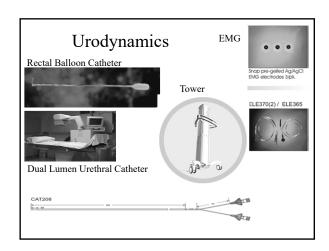


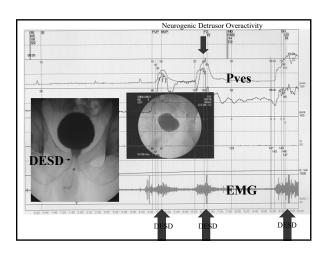
Cystoscopy seeking stones, foreign body, obstructing prostate or fistula, stricture fistula, tumor, or urethral diverticulum should be performed

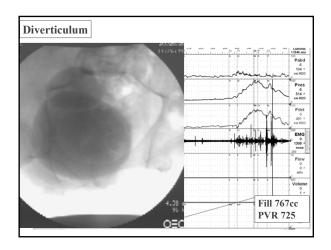


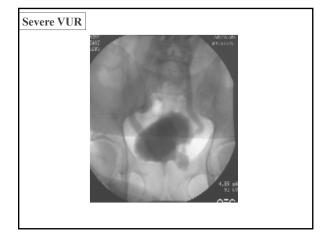
#### Urodynamics

- Should be performed in most patients with recurrent UTI in the setting of spinal cord injury
- Patients with stroke, Parkinson's disease, and multiple sclerosis who have bladder dysfunction and/or recurrent UTI









#### **UTI** Management

- Symptoms of:
  - Frequency
  - Urgency
  - Burning with urination
- Cloudy or Bloody Urine
- Odor
- Spasticity
- Fatigue
- · Altered Mental Status

#### Bacteria in NGB

- The microbiome of patients with neuropathic bladder is intrinsically different from those with normal functioning bladders.
- Lactobacillus is the prevalent species in healthy women and Corynebacterium in men
- Enterobacteriaceae species, which includes E. coli and Klebsiella, is the most prevalent in neurogenic bladder<sup>15,16</sup>.
- Patients in the hospital are more likely to have Pseudomonas, Acinetobacter, and Enterococcus species with extensive resistance patterns. These data warrant avoidance of treating urinary infections until the susceptibilities of the target organism are known.

Fouts DE, Pieper R, Spalkowski S, et al. Integrated next-generation sequencing of 165 fDNA and metaproteomics differentiate the healthy urine microbiome from asymptomicat bacterium in an energative Studies accusated with spin cord singsr, Journal of Translational Medicine. 2012;10:174.

Levy, J. Berton, F. L., Joussee, M., Haddad, R., Verollet, D., Guinet-Lacoste, A., & Amarenco, G. Bacterial ecology and antibiotic resistance in patients with neurogenic overactive bladder treated by bottliman toxin injections. Annals of Physical and Rehabilitation Medicine. 2013 56.

Hyama, Y., Takahashi, S., Ushara, T., Hashimoto, J., Nishinaka, K., Kitamura, H., & Masumori, N. Emergence of antinicrobial-resistant urepathogens instead from pediatrie patients with cystis on daily clean intermittent ratheterization. Journal of Infection and Chemotherany. 2015; 21(10), 703-706.

#### **Duration of Antibiotics**

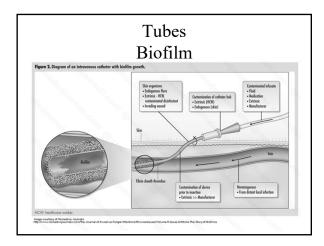
- Guidelines recommend a 7 day course for those who have prompt resolution of symptoms.
- If delayed response, 10-14 days is appropriate course.
- Indwelling catheters should be exchanged in the setting of infection to obtain the specimen off the new catheter and to improve the likelihood of successful treatment
- In difficult cases, consider changing the indwelling catheter a second time once on appropriate antibiotics.

Hooton T et al: Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America, Clinical Infectious Diseases, Volume 50, Issue 5, 1 March 2010, Pages 625–663

#### **Antibiotic Prophylaxis**

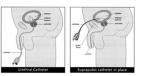
- Systemic antimicrobial prophylaxis should not be used for those with neurogenic bladder and recurrent UTIs.
- Several studies have examined the use of nitrofurantoin, fluoroquinolones, and trimethoprim/sulfamethoxazole as prophylaxis
- A Cochrane review concluded the benefits of antibiotic prophylaxis do not clearly outweigh the adverse effects such as antimicrobial resistance

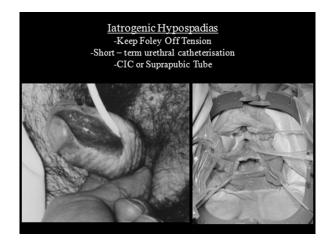
Niël-Weise, B. S., & Broek, P. J. (2005). Urinary catheter policies for long-term bladder drainage. Cochrane Database of Systematic Reviews.



#### UTI With Indwelling Catheter

- · Culture off new catheter
- · Cloudy
- Odor
- New leakage
- · Autonomic dysreflexia
- Pair
- Fever
- · Mental Status Change





#### Catheter Associated UTI

- · All UTIs in neurogenic bladder patients are considered "complex".
- In accordance with IDSA Guidelines, catheter-associated UTIs, which include indwelling and intermittent catheterization, are defined as the presence of clinical symptoms along with >10³ colony-forming units/mL of one or more bacterial species obtained from a clean catheterized specimen¹8.
- For those with indwelling catheters or suprapubic tube, the specimen should be
  obtained from the new tube after the catheter has been exchanged.
- Changing the catheter will improve the accuracy of identifying a culprit organism
  and also may improve the response to antibiotic therapy by removing the biofilm
  that serves as a scaffold for reinfection

Hooton T et al: Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America, Clinical Infectious Diseases, Wolme 50, Issue 5, 1 March 2010, Pages 625–663

Trautner BW, Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. American

#### Suprapubic Catheter

- Suprapubic catheter often becomes the management of choice for neurogenic bladder. This method is favored due to low-impact placement, reduced UTI risk and urethral complications versus urethral catheter, reversibility, and convenience for patients who cannot catheterize themselves. The use of antibiotics during the exchange did not alter the incidence of infection<sup>52</sup>; thus, the use of antibiotics at the time of catheter change is not recommended.
- Consider changing the catheters monthly, or earlier if indicated (clogging, symptomatic infection), as this allows for elective changes and avoidance of morbidity.
- Lastly, catheters used for suprapubic drainage should be larger bore (18-22
  French), flexible for comfort, and short-tipped to prevent erosion of the
  bladder surface.

Sorokin, Igor, and Elise De. "Options for Independent Bladder Management in Patients with Spinal Cord Injury and Hand Function Prohibiting Intermittent Catheterization." Neurourology and Urodynamics, vol. 34, no. 2, 2013, pp. 167–176., doi:10.1002/nau.22316.

#### Biofilm

- There are two routes of <u>biofilm</u> development on indwelling catheters: intraluminal and extraluminal. Intraluminal biofilm formation occurs when organisms gain access to the internal lumen of the catheter through failure of the closed drainage system or contamination of the collection bag.
- A closed-catheter drainage system should be used to reduce urinary infections.
- There is inadequate evidence to recommend single-use or daily change of urinary leg drainage bags to reduce UTIs <sup>59</sup>; consider a leg bag changing interval between 5 days up to 1 month
- Randomized controlled trials to establish the optimum time interval between changing drainage bags are needed.

Cottenden, A. et al. Management Using continence products (2017). Incontinence (6th ed.). Bristol, UK: International Continence Society.

Ostaszkiewicz, Jaterson J. Nurses' advice regarding sterile or clean urinary drainage bags for individuals with a long-ten indwelling urinary catheter. J Wound Ostomy Continence Nurs. 2012 Jan-Feb;39(1):77-83.

#### **Antimicrobial Coatings**

 Long-term catheterization (>30 days) was assessed in a Cochrane review of randomized trials, but the authors were unable to report a definitive conclusion due to inadequate evidence<sup>68</sup>

Jahn P, Preuss M, Kernig A, et al. Types of indwelling urinary catheters for long-term bladder drainage in adults. Cochrane Database Syst Rev. 2007pg. CD004997.

#### Irrigation

- Antibiotic Irrigations conflicting data to support this technique. Individual clinicians do employ irrigation strategies with select patients. Examples include Gentamycin, Neomycin, and simply saline.
- · Meta-analysis of intravesical aminoglycoside treatment :conflicting data.
- Review of seven retrospective European studies suggests irrigation with hyaluronic acid and chondroitin sulphate decrease the frequency of UTIs (restoring the glycosaminoglycan bladder layer).
- Guidelines recommend against the use catheter irrigation with antimicrobial agents due to conflicting data.

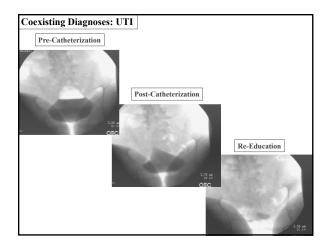
Van Nicewkoop C, Den Exter PL, Elzevier HW, Den Hartigh J, Van Dissel JT. Intravesical gentamicin for recurrent urinary tract infection in patients with intermittent bladder catheterisation. International Journal of Antimicrobial Agents. 2010; 36 (6): 485-90.

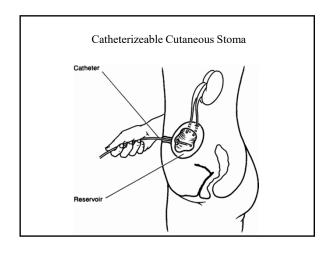
National Clinical Guideline. Centre (NGE) (UK). Infection Prevention and Control of Healtheare-Associated Infections in Primary and Community Care: Partial Update of NICE Clinical Guideline. Prevention and Control Feathbare-Associated Infections in Primary and Community Care: Partial Update of NICE Clinical Guidelines. No. 139: 10, Long term transpray catherists. https://www.ncbl.inlm.him.bev/besc/NBIKL192 (UK); 2012 Mar. (NICE Clinical Guidelines, No. 139: 10). Long term transpray catherists in the Nice Provides of the International Provinces and State Control of Control of Provinces of Carl International Technical Provinces and Provinces and

#### **Intermittent Catheters**

- Several <u>intermittent catheter techniques</u> have been evaluated for risk of UTI
- The largest Cochrane review and meta-analysis found no superior method to prevent UTIs.
- The cost of catheters, limited third-party insurance reimbursement, and increased environmental waste are issues associated with single use, sterile catheters.
- The Cochrane conclusions are to allow patient preference to guide management.
- Traditionally catheters with a siliconized or polyvinyl chloride, non-prelubricated, non-hydrophilic surface have been rewashed without evidence of inferiority.
- For patients who rewash catheters, the authors recommend changing to a new catheter every week, washing with water and clear-rinsing dish soap, then drying the catheter in open air.
- Alternatively, for convenience some patients use reusable catheters at home and single use catheters while out.

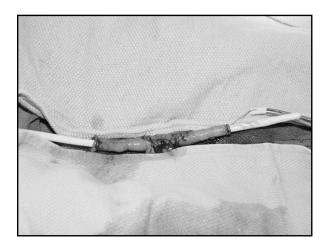
Bermingham SL, Hodgkinson S, Wright S, Hayter E, Spinks J, Pellowe



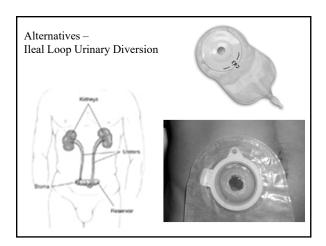












#### Proanthocyanidins "Cranberry"

• There is conflicting literature regarding cranberry supplements, in part due to the significant heterogeneity and lack of standardization of the supplements as well as the clinical outcomes evaluated (i.e., complicated or recurrent UTIs)

Mody L, Juthani-Mehta M. Urinary Tract Infections in Older Women: A Clinical Review. JAMA. 2014;311(8):844-854. Liska DJ, Kern HJ, Maki KC. Cranberries and Urinary Tract Infections: How Can the Same Evidence Lead to Conflicting Advice? AdV Nutr. 2016 May 16;7(3):498-506

#### **Probiotics**

• A 2015 Cochrane Review examined 9 quasirandomized controlled trials and randomized controlled trials evaluating the use of probiotics, predominantly Lactobacillus species. They concluded that there was no significant benefit demonstrated for probiotics, but because there was insufficient data, a benefit could not be ruled out 91

Schwenger EM, Tejani AM, Loewen PS. Probiotics for preventing urinary tract infections in adults and children. Cochrane Database Syst Rev. 2015 Dec 23;(12):CD008772

#### Other Orals

- Ascorbic acid alkalization of urine conflicting data
- <u>Methenamine salts</u> convert to formaldehyde in acidic urine, which then exhibits nonspecific antiseptic activity that is dependent on dwell
- <u>D-mannose</u> inhibiting bacterial adherence to urothelial cells by blocking Type 1 fimbriae

#### Vaccines/ Immunostimulants

- **OM-89** oral immunostimulant 18 different serotypes of heat-killed uropathogenic *E. Coli*, thought to decrease recurrent UTIs by stimulating innate immunity
- Vaginal vaccine available in Europe, is a vaccine incorporating 10 heat-killed uropathogenic E. Coli, Proteus vulgaris, Klebsiella pneumonia, Morganella morganii, and Enterococcus faecalis
- Intranasal vaccine based on adhesin proteins in uropathogenic E. coli and P. mirbalis

Wagenlehner FM, Ballarini S, Pilatz A, Weidner W, Lehr L, Naber KG. A Randomized, Double-Blind, Parallel-Group, Multicenter Clinical Study of Escherichia coli-Lyophilized Lysate for the Prophylaxis of Recurrent Uncomplicated Urinary Tract Infections. Urol Int. 2015;95(2):167-76. Uchling DT, Hopkins WJ, Elkawaji JE, Schmidt DM, Leverson GE. Phase 2 clinical trial of a vaginal mucosal vaccine for urinary tract infections. J Urol. 2003 Sep;170(3):867-9.

habibi M, Asadi Karam MR, Bokregozar MA, Oloomi M, Jafari A, Bouzari S. Intranasal immunization with fusion protein MrpH-FimH and MPL adjuvant confers protection against urinary tract infections caused by uropathogenic Escherichia coli and Proteus mirabilis. Mol Immunol. 2015 Apr;64(2):285-94.

#### Conclusion

- The improvement in care for persons with neurogenic bladder over the last several decades has improved renal morbidity, mortality, and overall quality of life.
- A combination approach including management of anatomic and functional factors with careful medical intervention can significantly improve frequency of urinary infection.
- Further study of non-antibiotic therapeutic strategies are much needed as we recognize the complexity of the urinary biomes and the limitations of antibiotic therapies.

#### PREVENTING HEALTHCARE-ACQUIRED CATHETER-ASSOCIATED URINARY TRACT INFECTIONS

Lona Mody, MD, MSc Amanda Sanford Hickey Professor of Medicine Division of Geriatric and Palliative Medicine, University of Michigan, Ann Arbor @LonaMody



Funding/Support provided by the NIA, CDC, AHRQ and non-profit foundations

#### OUTLINE

- Strategies to preventing Catheter-associated UTI (CAUTI) in:
  - Hospitalized patients
- Post-acute and long-term care patients
- · Non-infectious complications of indwelling urinary catheters
- Appropriate indwelling urinary catheter use in peri-operative period

#### INDWELLING URINARY CATHETER USE IN HOSPITALS AND SKILLED NURSING FACILITIES

- · Hospitalized patients
  - 5, 534 hospitals in US with 900K admissions/yr.
  - ~ 30% (ICU > non-ICU) with indwelling urinary catheters
  - 1 to 1.5 million catheter-days/yr.
- Skilled nursing facility patients
  - 15, 200 facilities with 1.4 million individuals any given day
  - 5% with indwelling urinary catheters (~ 70,000)
  - average 100 days/catheterized resident
  - 7 million catheter-days/yr.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 181

JUNE 2, 201

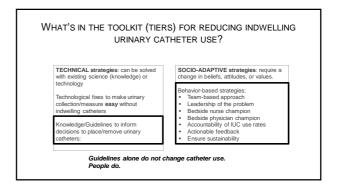
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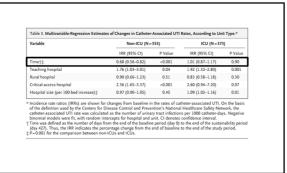
A Program to Prevent Catheter-Associated Urinary Tract Infection in Acute Care

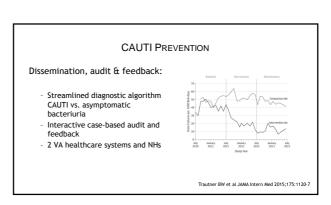
Sanjay Saint, M.D., M.P.H., M. Todd Greene, Ph.D., M.P.H., Sarah L. Krein, Ph.D., R.N., Mary A.M. Rogers, Ph.D., David Ratz, M.S., Karen E. Fowler, M.P.H., Burbara S. Edson, R.N., M.B.A., M.H.A., Sam R. Watson, M.S.A., C.P.P. Saphran Meyer-Losse, M.D., M.H.S.A., Marier Massaga, R.N., M.S.N., Kelly Faulkner, M.S.P.A., Carolyn V. Gould, M.D., M.S.C.R., James Battles, Ph.D., and Mohamad G. Fakin, M.D., M.P.H.

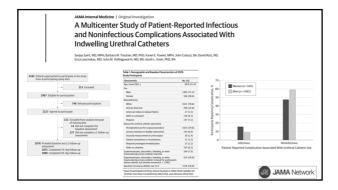


## WHAT'S IN THE TOOLKIT (TIERS) FOR REDUCING INDWELLING URINARY CATHETER USE? TECHNICAL strategies: can be solved with existing science (knowledge) or technology Technological fixes to make urinary collection/measure easy without indwelling catheters: SOCIO-ADAPTIVE strategies: require a change in beliefs, attitudes, or values. Behavior-based strategies: Team-based approach Leadership of the problem Bedside nurse champion Bedside physician champion Bedside physician champion Bedside physician champion Cacountability of III Cus arates Actionable feedback Ensure sustainability







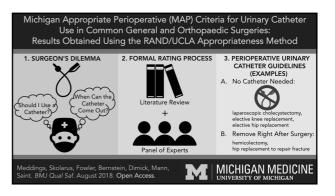


#### MICHIGAN APPROPRIATE PERIOPERATIVE (MAP) CRITERIA FOR URINARY CATHETER USE

- Used the RAND/UCLA Appropriateness Method to assess the appropriateness of urinary catheter placement and timing of removal for common adult general and orthopedic surgeries
  - Review of existing literature
  - Development of clinical scenarios
  - Expert panelists rated appropriateness 1<sup>st</sup> individually, then again in person after group discussion

#### **RESULTS**

- Appropriateness of catheter use varied by expected procedure time, expected intravenous fluids, and procedure-specific risks
- Summarized ratings into 3 groups:
  - 1. Can perform surgery without catheter
  - 2. Use intraoperatively only, ideally remove before leaving OR
  - 3. Use intraoperatively and keep catheter until post-op day 1 to 4



RECOMMENDATIONS FOR SAMPLE SURGERIES

Can Perform Surgery without Catheter

Laparoscopic cholecystectomy
Open appendectomy
Unilateral elective total hip arthroplasty
Unilateral total knee arthroplasty

A Targeted Infection Prevention Intervention
in Nursing Home Residents With Indwelling Devices
A Randomized Clinical Trial

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TARGETED INFECTION PREVENTION (TIP) STUDY

Design: Cluster-randomized trial Facilities: 12 NHs in SE MI

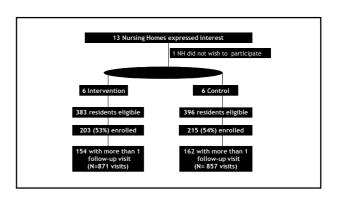
Population: Residents with indwelling urinary

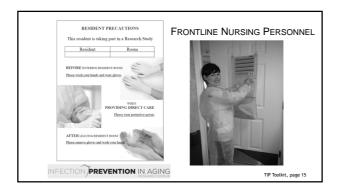
catheters and/or feeding tubes

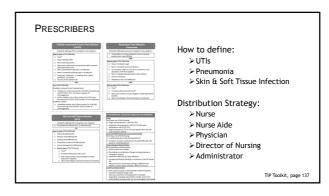
**Duration**: 2010-2013

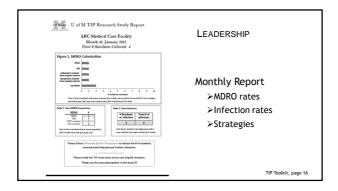
**Inclusion**: Device > 72 hrs., Informed consent

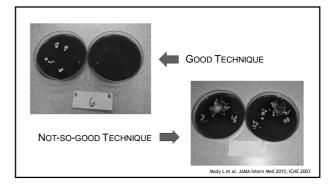
Exclusion: Hospice care

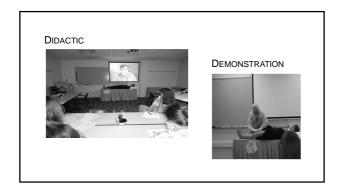








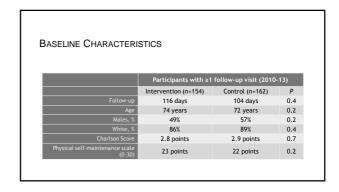


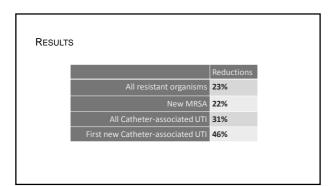


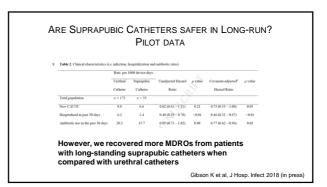


#### **MEASURES**

- Outcomes:
  - MDRO prevalence
  - Incident MDROs (new acquisitions)
  - Device-related urinary tract, upper respiratory tract infections
    - Clinical definitions







HOW MUCH WOULD CAUTI PREVENTION PROGRAMS COST?

Economic Evaluation of a Catheter-Associated Urinary Tract Infection Prevention Program in Nursing Homes

Dead W. Battler, PRD. \* Sent L. Even, PRD. R. V.\* Samps Saide, MD. MPJ.\*

Nicholas Coren, PRD.\*\* Alory Solik, RS.\* Reymould Lymm, RA. \* and Leas Mody, MD. MSC\*\*\*\*\*\*

\* CAUTI Prevention Program Cost: 20K/year

\* Most savings come from fewer CAUTI-related hospitalizations

\* 0.197 gain in quality-adjusted life-years

IMPLEMENTATION: SCALING UP

Collaborative approach:

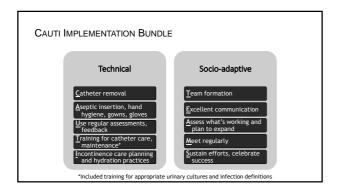
Address a specific infection or safety concern

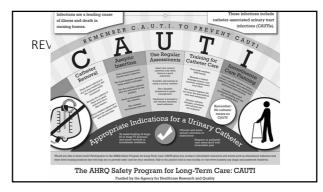
Recruit teams from multiple organizations

Work in a structured fashion over a limited period

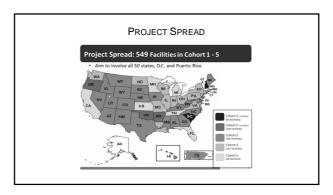
Narrow gap between best and actual practice

Saint S et. al NEJM 2016;374:2111-9







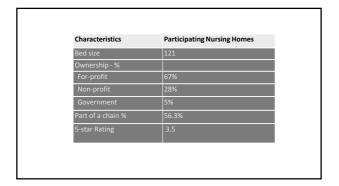


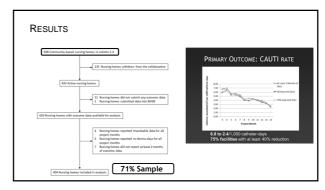
#### **OPERATIONALIZING THE INTERVENTION**

- Educational events
- 4 Onboarding Webinars, study start 4 Training Module Webinars, study start
- Content Webinars, monthly
- Coaching Calls with data feedback, monthly
   Organizational Lead calls to discuss implementation, monthly
- 3 Learning Sessions (in-person or web-based)
- Site visits
- Materials: Videos, power point presentations with notes, easy to use tools,  $train-the-trainer\ materials, facility\ Implementation\ Guide\ and\ LTC\ Toolkit$

#### DATA COLLECTION, OUTCOMES

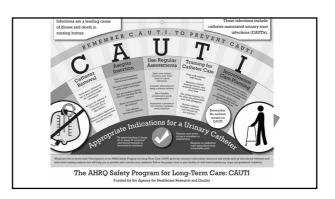
- Facility collected:
  - # residents (census)
  - # residents with an indwelling catheter
  - # residents with a CAUTI (per CDC/NHSN definition)
  - # of urine cultures ordered at the facility
- Primary Outcome: No. CAUTI/1,000 catheter-days
- Secondary Outcome: Catheter utilization ratio
- Exploratory Outcome: Urinary culture rate/1,000 resident-days





#### THE 'ABCDE' OF CAUTI PREVENTION IN HOSPITALS

- A dherence to general infection control practices (e.g. hand hygiene, surveillance and feedback, aseptic insertion, proper maintenance, education)
- **B** ladder ultrasound to guide decision making
- **C** ondom catheters, intermittent catheterization should be considered when appropriate
- $\boldsymbol{D}$  o not use indwelling catheter unless you must!
- **E** arly removal of the catheter using a reminder or nurse- initiated removal protocol



#### REMEMBER!

- CAUTI prevention is a 'team sport'
- Engage with infection prevention teams and quality improvement initiatives at your institution

## BPS/IC 2018: The Emperor has no clothes

Christopher K. Payne, MD
Vista Urology & Pelvic Pain Partners
Emeritus Professor of Urology at Stanford

#### **Disclosures**

- Advisory Role: Avadel, Aquinox, Astellas, Myoforte
- Ownership Interests: Vista Urology & Pelvic Pain Partners

#### **Outline**

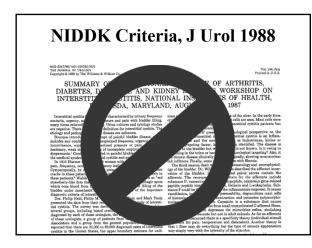
- IC/BPS: Where did we go wrong?
- What do we know about these patients?
- How should we approach this now?
- Future directions (throughout)

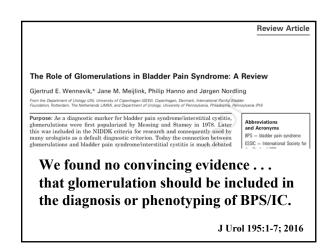


# Where Did We Go Wrong? INTERSTITIAL Early Dis MESSING, M.D. TH STAMEY, M.D. F stanford University School of Calfornia ABSTRACT— uspective rector repetedly sterile use cyclology must be a construction of the beautiful such patients as a cert form of the construction of the beautiful such patients as a cert form and canodilation. The distribution of the bid and a Humor's alone in the construction of the bid and a Humor's alone in the stand canodilation. The colls is variable, and even felped and even for the patients of the patients o

#### Where Did We Go Wrong?

- Started with an attractive THEORY
  - "We believe"
  - "Retrospective Review"
- Deserved testing
- Adopted without question

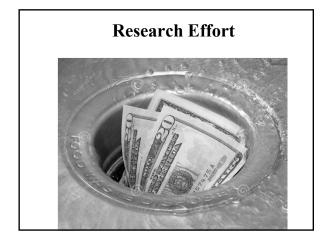


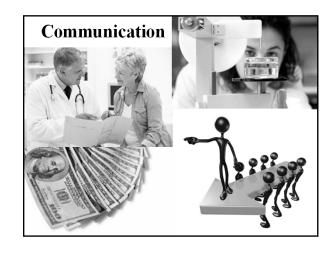


#### So what?

- There isn't anything better
- IC/BPS is good enough until we figure it out.
- Everyone knows it isn't exactly right
- No one really cares about it anyway

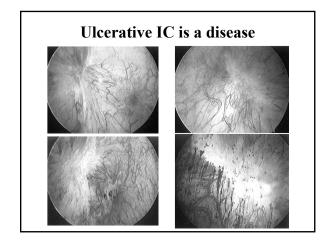


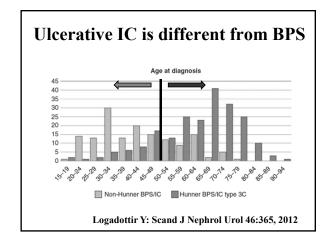


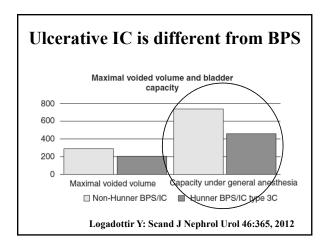


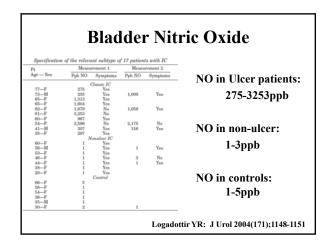
## What do we know about these patients today?

- Ulcerative Interstitial Cystitis is a unique, specific disease.
- Bladder Pain Syndrome is not a disease; it is a syndrome.









Infection/Inflammation

Discovery of Morphological Subgroups
That Correlate With Severity of Symptoms in
Interstitial Cystitis: A Proposed Biopsy Classification System

Benjamin E. Lolby, J. Richard Landis, \*Kathleen J. Proport, John E. Tomaszewski† and the
Interstitial Cystitis Data Base Study Group

Pross the University of Pennipumis School of Medicine, Philadelphia, Pennipumis

Purpose: We identified morphologically distinct subgroups in interstitial cystitis using cluster analysis and investigated the
associations between cluster membership and urinary symptoms.

Materials and Methods of 637 patients enrolled in the Interstitial Cystitis Data Base Study 203 (32%) provided bladder
biogosis at baseline servening, representing the ficus of this analysis. A cluster analysis algorithm implemented in SASB

Interpolational fastures was used to construct subgroups of these patients. Multivariate regression models for baseline
nighttime and 24-hour voiding frequency, urinary urgency and pain were developed, incorporating indicator variables for
cluster membership as predictors. Longitudinal urinary symptoms profiles during 3 years of followup were also compared
among the morphology clusters.

Results Three emphology clusters were identified, corresponding to unique pathological groupings. In cluster C<sub>4</sub>.7 patients
school multiple pathological features of parenchymal damage, including several inflammatory features. In cluster C<sub>4</sub>.17
school multiple pathological features were present above the specified thresholds for C<sub>5</sub>. Cluster membership was significantly
associated with baseline nighttime and 24-hour frequency (p < 0,001, and with urinary urgency p = 0,003. These significant
increases in baseline symptoms servity among clusters from C<sub>5</sub> to C<sub>5</sub> to C<sub>5</sub> persisted throughout the 3 years of followup.

Conclusione These results suggest an important role for histopathological features were as followup.
Conclusione These results suggest an important role for histopathological features in the predictive modeling of

#### Morphological Subgroups of IC

- 203 biopsies, 39 pathologic factors
- 3 subgroups identified by cluster analysis
  - -7 patients with multiple pathological features of parenchymal damage
  - -17 complete denudation, variable edema
  - 179 none of the pathologic features were present above the specified thresholds

Leiby BE, et. al.: J Urol 2007;177: 142-148

#### Reflect on this a bit



#### No pathologic abnormality

#

#### Chronic inflammatory disease

#### **Ulcerative Interstitial Cystitis**

- This is a unique, fascinating, serious disease.
- Many more questions than answers:
  - Histopathologic subtypes
  - Prognosis
  - Optimal medical/surgical therapy
- If we study it we can solve it.

### What do we know now: BPS is a syndrome

"A syndrome is a set of medical signs and symptoms that are correlated with each other and, often, with a specific disease."

#### **Common Syndromes**

- Bladder Pain Syndrome
- Head Pain Syndrome
- Chest Pain Syndrome

A syndrome is not a diagnosis. It is a starting point on the path to a diagnosis.

### BPS is not well treated without making a more specific diagnosis

My patient has chronic head pain. Should I follow the ANA treatment algorithm?

- 1. Acetaminophen
- 2. Sumatriptan
- 3. Physical therapy
- 4. Botox injections
- 5. Brain surgery



#### **Phenotyping Untangles the Mess**



#### **Relevant BPS Phenotypes?!**

- True Bladder Phenotype
- Myofascial Phenotype
- Pudendal Neuropathy Phenotype
- Central Sensitization Phenotype

Much room for research & refinement

#### **Bladder Phenotype**

- What we all learned—pain on bladder filling relieved by urination
- Consistently reduced volumes on diary
- Primary bladder tenderness on exam
- Pain relief with intravesical lidocaine

#### **Myofascial Phenotype**

- Often clear provocative factor
- Often other orthopedic issues
- Pain less clearly related to bladder
- Myofascial tender points > bladder, NOT only in pelvic floor
- Bladder diary shows many normal volume voids, especially overnight

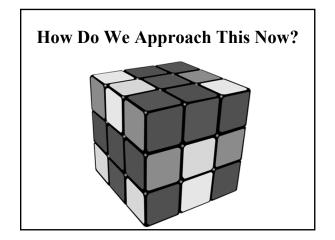
#### **Pudendal Neuropathy Phenotype**

- · Pain with sitting
- Specific sensory findings on exam
- Tinel sign over pudendal nerve
- Bladder symptoms less consistent and volumes not always reduced

#### **Systemic Pain Phenotype**

"overlapping functional somatic syndrome including fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, chronic headache, and allergies"

**Anxiety, Depression, Catastrophizing** 

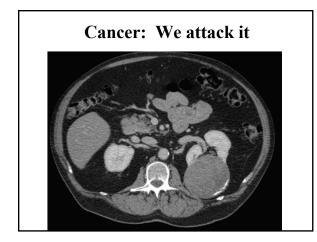


An Oncologic Approach to Interstitial Cystitis/Painful Bladder Syndrome

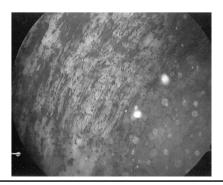
Christopher K. Payne, MD

Urology Rounds University of Pennsylvania 2012

> Payne CK. Curr Bladder Dysf Reports March 2015;10(1), pp 81-86.



IC: We run from it!



IC as a Cancer

IC QoL is worse than most other chronic diseases

#### **Adopt from the Oncologist**

- Seriousness of purpose
- Optimistic but realistic approach
- Continuous critical evaluation
- Partnership approach involving the patient

#### What to Say?

#### Wrong

- Incurable disease
- Gets worse and worse over time
- Never eat these foods again

## DANGER DANGER POISON

#### What to Say?

#### Wrong

#### Right

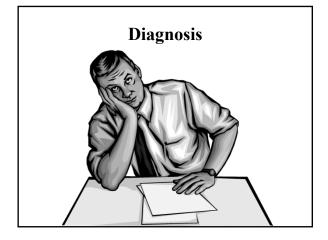
- · Incurable disease
- We don't understand the cause so there is no one cure
- Gets worse and worse
- Usually changes very little over the years.
- You will never be able to eat these foods again
- You should determine if any foods make your symptoms worse

Getting well requires hard work & determination!



#### The Oncologic Approach

- Diagnosis
- Staging
- Treatment
- Follow-up
- Cure



#### **Diagnosis: Initial Classification**

- Does this patient have ulcerative IC?
- Does this patient have BPS? If so, what is the source of the pain?

History Physical Urinalysis/culture Bladder diary

#### **Interstitial Cystitis Diagnosis**

- Cystoscopy
- Hydrodistention
- Biopsy
- Cytology

#### **Diagnosis of BPS (Phenotyping)**

- · Diagnosis conveys what is known
- · Careful, thorough approach
  - Oncologist "rules in" cancer by biopsy
  - We mostly "rule out" other disorders
- The evaluation is individualized to the unique circumstances of each patient

#### **Current Definition BPS**

"An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than 6 weeks duration, in the absence of infection or other identifiable causes"

Neurourol Urodyn. 2009;28(4):274-86

#### **ESSIC Approach**

The diagnosis of BPS is thus made on the basis of exclusion of confusable diseases and confirmation by the recognition of the presence of the specific combination of symptoms and signs of BPS. If the main urinary symptoms are not explained by a single diagnosis (confusable disease or BPS), the presence of a second diagnosis is possible.

van der Merwe JP et. al.: Eur Urol 2008

Confusable disease	Excluded or diagnosed by <sup>a</sup> Cystoscopy and biopsy	
Carcinoma and carcinoma in situ		
Infection with		
Common intestinal bacteria	Routine bacterial culture	
Chlamydia trachomatis, Ureaplasma urealyticum	Special cultures	
Mycoplasma hominis, Mycoplasma genitalium		
Corynebacterium urealyticum, Candida species		
Mycobacterium tuberculosis	Dipstick; if "sterile" pyuria culture for M. tuberculosis	
Herpes simplex and human papilloma virus	Physical examination	
Radiation	Medical history	
nemotherapy, including immunotherapy with cyclophosphamide Medical history		
Anti-inflammatory therapy with tiaprofenic acid Medical history		
Bladder-neck obstruction and neurogenic outlet obstruction	Uroflowmetry and ultrasound	
Bladder stone	Imaging or cystoscopy	
Lower ureteric stone	Medical history and/or hematuria: upper urinary tract	
	imaging such CT or IVP	
Urethral diverticulum	Medical history and physical examination	
Urogenital prolapse	Medical history and physical examination	
Endometriosis	Medical history and physical examination	
Vaginal candidiasis	Medical history and physical examination	
Cervical, uterine, and ovarian cancer	Physical examination	
Incomplete bladder emptying (retention)	Postvoid residual urine volume measured by ultrasound scanning	
Overactive bladder	Medical history and urodynamics	
Prostate cancer	Physical examination and PSA	
Benign prostatic obstruction	Uroflowmetry and pressure-flow studies	
Chronic bacterial prostatitis	Medical history, physical examination, culture	
Chronic non-bacterial prostatitis	Medical history, physical examination, culture	
Pudendal nerve entrapment	Medical history, physical examination, nerve block may prove diagnosis	
Pelvic floor muscle-related pain	Medical history, physical examination	

#### **Diagnosis: Other Testing**

- As per ESSIC, as needed to rule out other disorders
- Individualized

Imaging Urodynamics Cystoscopy

#### **Staging & Grading**

- Oncologists are fanatical about this
- Description is rational
- Evolves with evidence
- · Relevant to treatment approach

Neither IC nor BPS have an inherently progressive course

#### **Staging Ulcerative IC**

- Bladder capacity under anesthesia
- Number, size of ulcers
- Scarring/distortion of bladder

#### **Staging Ulcerative IC**

• Stage 1: >600cc

• Stage 2: 400 to 600cc

• Stage 3: 300 to 400cc

• Stage 4: <300cc

#### **Grading Ulcerative IC**

• Interval to recurrence following surgery

#### **Grading Ulcerative IC**

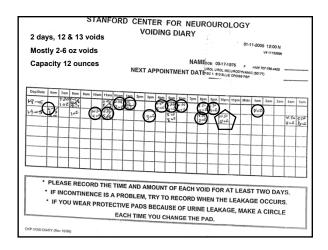
• Grade 1: > 1 year remission

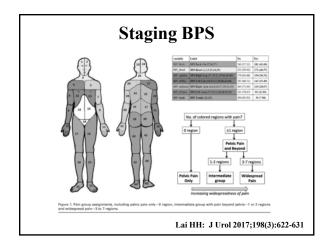
• Grade 2: 6-12 months remission

• Grade 3: <6 months remission

#### **Staging BPS**

- Bladder capacity by diary
- Objective symptom scores

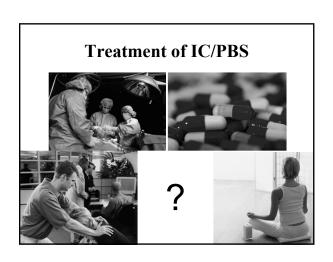


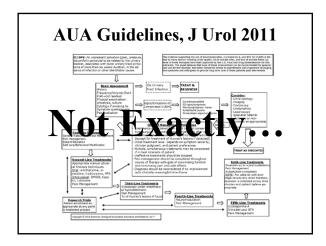


#### **Staging BPS**

- 424 patients with pain maps:
  - -25% only pelvic pain
  - -38% pelvic pain and beyond (1-2 regions)
  - -38% widespread pain (3-7 regions)
- Correlates strongly with CS
- Phenotype or Stage????

Lai HH: J Urol 2017;198(3):622-631





#### **Basic/Behavioral Therapies**

- Dietary magnetic (ICN Food List App)
- Bladder raining
- Genera ealth p es/self re
  - Exerci tre
  - Meditat xation

#### First Liberapy

- I sical Therap
- · ral Therapy
- Amitripty
  Pentos sulfate
- Astillation
- · L er distenti

#### **Secondary Options**

- Alterp ies
- Pair
- M .gement/Ref
- Ir Stim
- er intray
- · It w pressive
- · One dinum to
- · Radica.

#### **Treatment**

- Oncologists know exactly how to use their tools, IC drugs used haphazardly
- Oncologists set a plan for each treatment with specific expectations
- Oncologists evaluate every treatment
- Combination therapy is great . . . when each agent is adding effect.

#### **Treatment of Ulcerative IC**

- Ulcerative IC primarily a surgical disease
- Surgery necessary to establish:
  - Diagnosis
  - -Stage
  - Grade
- Treatment aimed at restoring normal bladder function

#### **Surgical Treatment of IC**

- Distention and fulguration
- Injection of steroids

#### **Adjuvant Treatment of IC**

#### Treatments aimed at the bladder

- Urinary analgesics/bladder training
- Bladder instillations
- Pentosanpolysulfate
- Cyclosporine

#### **Treatment of BPS**

- Treatment focused on phenotype
- Each treatment is also a test

#### **Treatment Principles**

- One major intervention at a time
- Have a clear plan for each intervention
- Evaluate every intervention subjectively and objectively
  - Symptom score
  - Bladder diary
- Expect to need combination therapy
- · Aim for objectively normal bladder

#### **Bladder Phenotype**

- Urinary analgesics
- Bladder instillations
- Pentosan Polysulfate
- · Pain Management
- Botulinum Toxin
- Neuromodulation

**Bladder Training always!** 

#### **Bladder training**

- Efficacy shown years ago by Blaivas
  - If pain reasonably controlled
- Rationale demonstrated by Chai & Keay
  - The distended bladder releases growth hormones
  - Would promote healing
- Involves and empowers the patient

#### **Myofascial Phenotype**

- · Yoga, stretching, pelvic drop
- Myofascial physical therapy
- Muscle relaxants
- · Pain management
- Trigger point injections
- Botulinum Toxin
- Neuromodulation?

#### **Pudendal Neuropathy Phenotype**

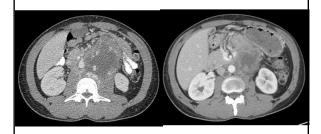
- Stop provocative behaviors
- Yoga, stretching
- Myofascial physical therapy
- Neuromodulating drugs/Pain management
- Injections
- Surgical release/Neurostimulation

#### **Systemic Pain Phenotype**

- Team approach—rare urologist who can take this on primarily
- Focus treatment on central sensitization
- · Look for untreated anxiety/depression.
- Only when Psych issues addressed should other therapy be instituted.
- · Therapy aimed at restoring ADL



#### **Assess the Outcome**



The mass has definitely responded but the oncologist will still recommend more therapy

#### **Remission?**

- Complete Remission:
  - Patient is content
  - No evidence of active disease
    - Normal bladder diary (400cc capacity)
    - No food sensitivities
    - No limitations on activities (exercise, sex)
- Partial Remission
  - Patient is content
  - Evidence of active disease
- Improved—everything else

#### **Remission! What next?**

- The oncologist does not stop therapy when the CT scan shows the lesion disappeared
- Just because we can't see it doesn't mean it is not there
- Consolidation therapy is important:
  - Confirm the good response
  - Normalize behaviors
  - Create expectation of success

#### **CURE**

- No oncologist starts off thinking about making the patient a little bit better
- No urologist approaches an IC patient with an intent to cure.
- Could that have something to do with our success??

#### What is "Cure"?

- Complete remission
- · Maintained off medical therapy

#### Suggest:

- 1. Maintain the remission for about 6 months
- 2. Titrate off successful therapies slowly
- 3. Start with therapy that causes side effects

## Five take-home points for managing IC and BPS

- 1. Ulcerative IC is a disease
- 2. BPS is not a disease; it is a syndrome
- 3. Don't think of IC & BPS the same way
- 4. Don't treat BPS without identifying the pain drivers—phenotyping
- 5. These are potentially curable diseases

#### **Summary Oncologic Approach**

- Adopt the attitude of the oncologist and think of IC as a serious but curable disorder
- Patient participates, sets goals, evaluates
- Emphasize objective assessment and reassessment with diary/symptom scores.
- Assess and document result of each treatment



#### Male Pelvic Pain NOT prostatitis

Jeannette M Potts, MD CoFounder Vista Urology San Jose, California

#### **Disclosures**

Advisory Role

- Aquinox
- Avadel
- Vista Urology



Traveled all over North America seeking help

"Seen" by 13 Urologists

Several courses of cipro, alpha blockers, NSAID's

Traveled all over North America seeking help

"Seen" by 13 Urologists

Several courses of cipro, alpha blockers, NSAID's

AND A HEFTY DOSE OF EMASCULATION

#### This condition is common

- ICD-9 code 601.1; most common urological dx in men <50
- "Prostatitis more common than BPH and prostate cancer combined."
- "...Will affect 50% of all men at some time during their lives"
- National and Global Prevalence up to 9.7%

#### **CONDITION IS MISNAMED**

## A LESSON IN NOMENCLATURE

## A LESSON IN NOMENCLATURE

#### **IMAGINE**

#### NIH Encephalitis Classification

- Category 1: Viral Encephalitis
- Category 2: Bacterial Encephalitis
- Category 3:
- Category 4: Asymptomatic with AbnI CSF

#### NIH Encephalitis Classification

- Category 1: Viral Encephalitis
- Category 2: Bacterial Encephalitis
- Category 3: **HEADACHE**
- Category 4: Asymptomatic with Abnl CSF

#### NIH Prostatitis Classification

- Category 1: Acute Bacterial Prostatitis
- Category 2: Chronic Bacterial Prostatitis
- Category 3 Chronic Pelvic Pain Syndrome
- Category 4: Asymptomatic/Histological

#### NIH Prostatitis Classification

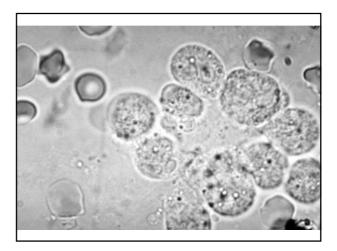
- Category 1: Acute Bacterial Prostatitis
- Category 2: Chronic Bacterial Prostatitis
- Categ 5 Chronic Pelvic Pain Syndrome
- Category 4: Asymptomatic/Histological

#### Category 3 Prostatitis

never proven to be caused by an infection nor a disease of the prostate.

NIDDK 1996

#### **ONCE UPON A TIME...**



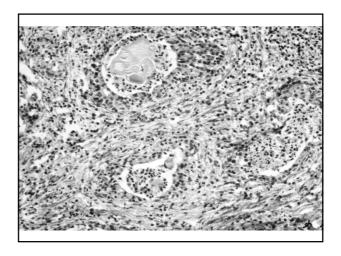
#### Significance of WBC's in EPS?

 Prostatic inflammation resolves after treatment in acute bacterial prostatitis, but is episodic in chronic and abacterial forms.

Wright, et al. J Urol, 1994

 Among asymptomatic men with elevated PSA, 42% had positive EPS

Potts. J Urol, 2000



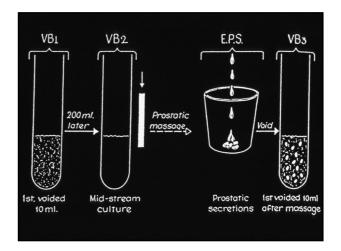
#### Inflammation Histologically?

 Among SYMPTOMATIC patients, inflammation was identified in only 5%

True, et al. J Urol, 1999

 Among ASYMPTOMATIC patients with elevated PSA up to 52%

Potts. J Urol, 2000



#### Significance of Bacteria

- Only 5-7 % of patients have positive bacterial cultures.
- 7% of controls have positive bacterial cultures!

Nickel, 2002

• State of the art Micro "Negative in CP/CPPS"

Nickel, AUA, 2013

#### What if it is a genuine infection?

- Signs or Symptoms
- Fever?
- U/A?
- Culture?
- Treatment?
- Follow Up?

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#### Use of Meares-Stamey Four-glass Test vs. Antibiotic Use Almost More than About Less than Rarely Never half half Meares-4% 33% 47% Stamey Anitibiotics 42% 4% 1% McNaughton Collins et al, Urol, 2000

#### Giessen Consensus

Withhold Antibiotics until there are TWO corroborative localization cultures

EuropeanUrol Supp, 2002

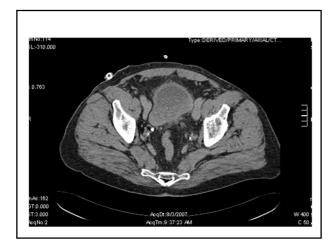
#### What if it is a genuine infection?

- Signs or Symptoms
- Fever?
- U/A?
- Culture?
- Treatment?
- Follow Up?

#### This is a complicated UTI

- Localization Culture
- Imaging
- Exclude obstruction/retention: Flow rate and residual
- Retrograde Urethrogram (RUG)
- Cystoscopy







#### Randomized Multicenter Feasibility Trial of Myofascial Physical Therapy for the Treatment of Urological Chronic Pelvic Pain Syndromes

Mary P. FitzGerald,\* Rodney U. Anderson,† Jeannette Potts,‡ Christopher K. Payne, Kenneth M. Peters,§ J. Quentin Clemens, ¶ Rhonda Kotarinos, Laura Fraser, Annemarie Cosby, Carole Fortman, Cynthia Neville, Suzanne Badillo, Lisa Odabachian, Andrea Sanfield, Betsy O'Dougherty, Rick Halle-Podell, Liyi Cen, Shannon Chuai, J. Richard Landis,\*\* Keith Mickelberg, Ted Barrell, John W. Kusek and Leroy M. Nyberg for the Urological Pelvic Pain Collaborative Research Network

J Urol 182:570, 2009

#### NIH Multicenter PT Trial

The only POSITIVE study in 15 years.

#### NIH Multicenter PT Trial

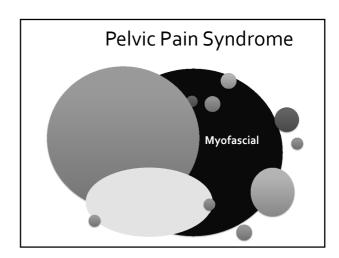
The only POSITIVE study in 15 years.

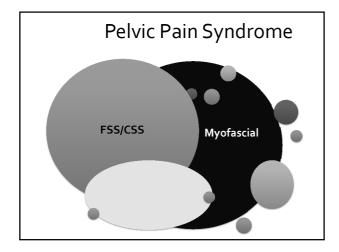
THE ONLY STUDY TO INCLUDE

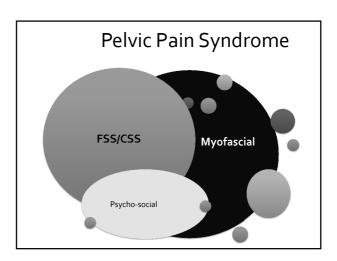
Thoughtful, methodical physical examination as inclusion criteria; ie **PHENOTYPING**.

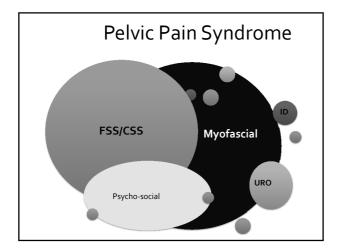
WE NEED TO CAREFULLY FORMULATE THE DIAGNOSIS BEFORE WE TREAT

WE NEED TO CAREFULLY FORMULATE THE DIAGNOSIS BEFORE WE TREAT OR STUDY!









Beyond the HPI and PMH....

SEARCH FOR FSS/CSS

#### Functional Somatic Syndromes

- Fibromyalgia
- Irritable Bowel Syndrome
- Proctalgia Fugax
- Non-ulcer Dyspepsia
- Chronic Fatigue
- Restless Leg syndrome
- Globus Syndrome

- Migraine Headaches
- Atypical Chest Pain
- Hyperventilation Syndrome
- TMJ Syndrome
- Interstitial Cystitis
- Multiple chemical sensitivity
- Gulf War Illness

## "Prostatitis" A functional somatic syndrome

Psyche-related Dx

48%

• Fnx Somatic Disorders

65%

(Population lifetime prevalence [Bass] 4%)

Potts et al, AUA,2001
Potts, Euro J Uro, suppl, 2003

#### "Prostatitis" A functional somatic syndrome

Psyche-related Dx

48%

• Fnx Somatic Disorders

65%

(Population lifetime prevalence [Bass] 4%)

Potts et al, AUA, 2001
Potts, Euro J Uro, suppl, 2003

#### CP/CPPS: Comorbidity

BJU 2005	CP=463	Cont=121	P value
urethritis	12%	4%	0.008
Cardiovasc	11	2	0.004
Neuro	41	14	<0.001
Psych	29	11	<0.001
Lymph/ heme/inf	41	20	<0.001

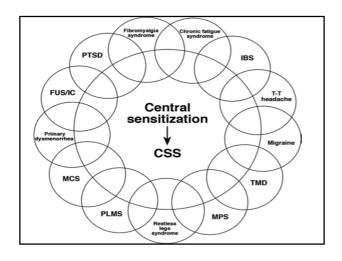
#### Impact of FSS/CSS

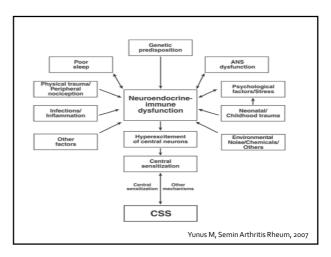
- Prevalence of FSS 4% (Bass, 2002)
- Somatic symptoms and syndromes account for 20-35% of outpatient consultations across all medical specialties (Wessely, 1999)
- US\$256 billion per year in medical care costs are "attributable to the incremental effect of somatization alone." (Barsky, 2005)

#### CP/CPPS: Co-Morbidity

- Annual cost > \$4,000, in US
- Greater healthcare cost than Rheumatoid Arthritis
- Cost differences between CP patients and typical HMO due to problems other than prostatitis.

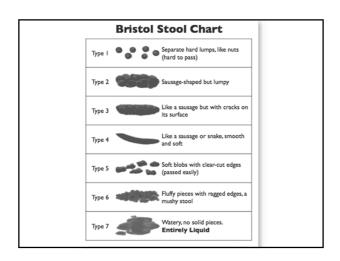
Calhoun et al. Arch Int Med, 2004 Turner et al. Urol, 2004











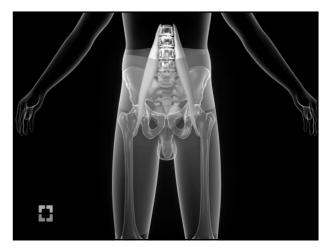


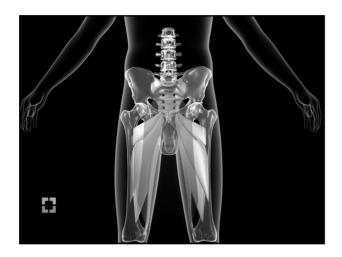
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**BEYOND THE ROUTINE EXAM...** 

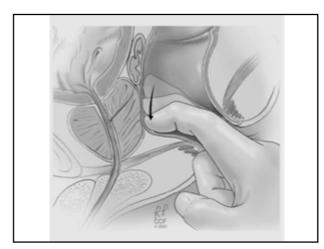


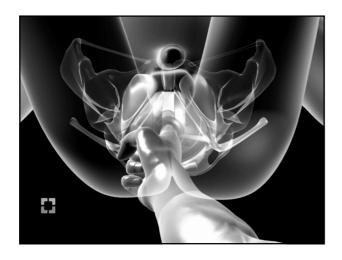


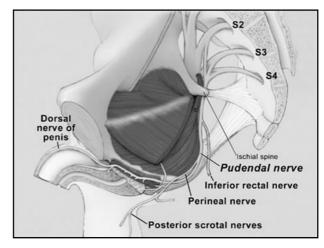


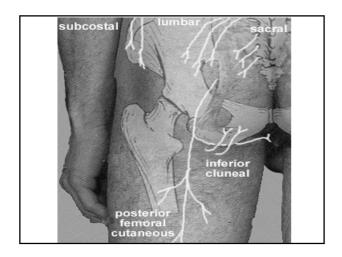


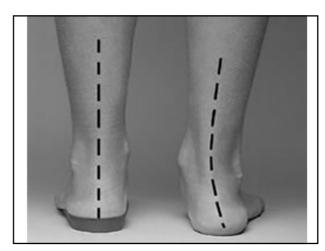


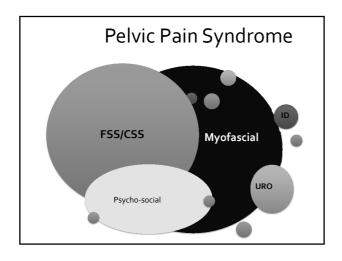












IF PATIENT DOES NOT IMPROVE START OVER- FROM SCRATCH

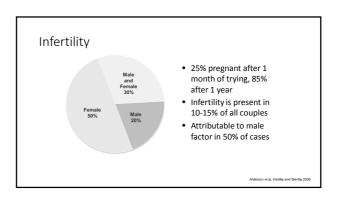
# Male Infertility C. Tanrikut, MD, FACS Reproductive Urologist, Shady Grove Fertility Georgetown University School of Medicine

#### Disclosures

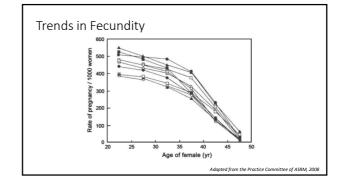
- Medical Director, Andrology Laboratory of New England Cryogenic Center
- Advisory Board, Ferring Pharmaceuticals
- \*Off-label medication use

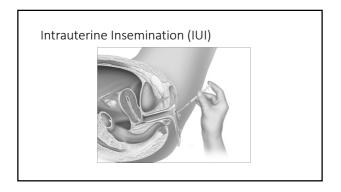
#### Objectives

- To provide a thorough understanding of male reproductive anatomy and physiology
- To discuss the rationale and approach to evaluation of the infertile male
- To explain treatment approaches for male factor infertility

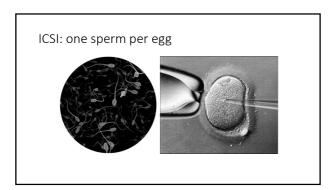


What does a urologist need to know about the female partner?

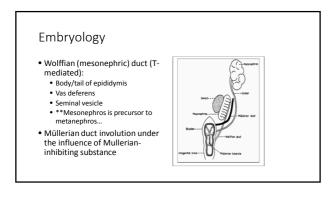


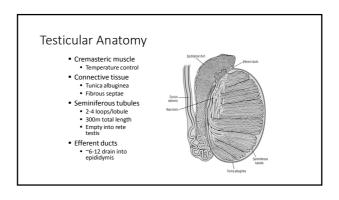






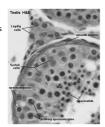
Back to Basics: Anatomy and Physiology





#### Testicular Anatomy

- Functional
- Endocrine function Leydig cells
   Exocrine function Sertoli cells
- Structural
  - · Intratubular compartment
    - Sertoli cells
       Germ cells
  - Germ cells
     Peritubular compartment
     Leydig cells
     Basement membrane
     Myofibroblasts
     Blood-testis barrier



#### Sertoli cells

- Polarized cells: extend from basement membrane to lumen
- Comprise 1/3 of bulk of germinal epithelium
- Responsible for blood-testis barrier
- Engulf and nurture developing germ cells
- germ cells

  Regulate tubule
  microenvironment (govern fluid
  secretions, phagocytosis,
  steroid metabolism, sperm
  production, and sperm
  movement/development)



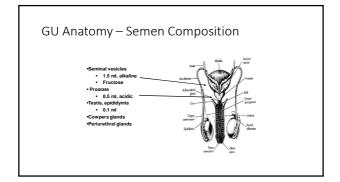
#### Synopsis of Leydig and Sertoli cell synergy

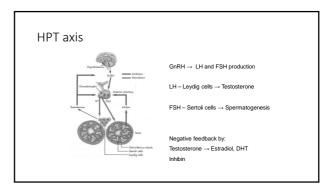
- What role do Leydig cells play in creating a favorable environment for sperm production?
  - Testosterone production in response to LH
     Paracrine effect on Sertoli cells

  - Testosterone concentration in testes ~100x peripheral serum concentration
- How do Sertoli cells support spermatogenesis?
  - FSH stimulates Sertoli cell function throughout life
     Create a specialized microenvironment

  - Expose germ cells to high levels of testosterone
     Transport differentiating germ cells toward the seminiferous tubule lumen

Timeframe of sperm production: ~2.5 mos 10-15 lobules





#### **Chief Complaint**

"My partner and I really want to have a baby – we've been trying for a year without success. Can you help us??"



#### History

- Prior fertility
- Sexual function: drive, erectile, ejaculatory
- Testis pain or swelling
- Cryptorchidism
- Prior inguinal or scrotal surgery, trauma
- Brothers' fertility history

#### Medications

- Calcium channel blockers
- Gout medications
- Cimetidine
- Sulfasalazine
- Exogenous testosterone
- ?finasteride
- (Alpha-blockers)

#### Social History

- Heat exposure
- Exercise
  - Anabolic steroids?
- Tobacco
- Alcohol
- Illicit drugs
- Lubricants

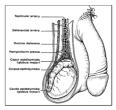
#### Physical Examination

- Body habitus
- Hair distribution
- Gynecomastia
- GU exam



#### GU Anatomy -- Exam

- Phallus
- Testes
- Epididymides
- Spermatic cord
  - Vasa deferentia - Varicocele



#### Hypogonadism

"Inadequate gonadal function, as manifested by deficiencies in gametogenesis and/or the secretion of gonadal hormones" (Stee

- Poor function of the testes

  - Diminished sperm production
     Decreased testosterone production
- Two basic causes

  - Problem with the testes
     Problem with the signals to the testes

#### Testing

- Semen Analysis
- Bloodwork
  - Serum endocrine studies
     (Genetic testing)
- [Imaging]

  - (Scrotal U/S)
     (Transrectal U/S)

#### Semen Analysis

- Volume
- pH
- Concentration (#sperm/mL)
- Motility
- Morphology

\*\*2-5 day abstinence interval



#### SA reference values – WHO 5<sup>th</sup> Ed. (2010)

- Volume ≥ 1.5cc
- Sperm concentration ≥ 15 mil/mL
- Sperm count ≥ 39 mil/ejaculate
- Motility ≥40% TM, ≥32% PM
- Morphology ≥ 4% (strict)

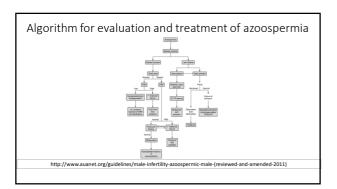
# Semen Analysis

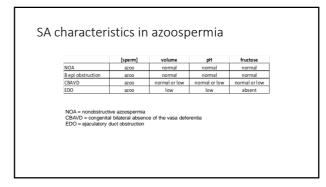
#### Male Infertility and Azoospermia

- Azoospermia = absence of sperm in ejaculate
  Identified in ~10-15% of infertile males
  (<2% of overall male population)
- Etiologies of azoospermia
   Production issue
   Primary hypogonadism ~60%
   intrinsic disorder of spermatoge
   Secondary hypogonadism (rare)
   Outflow issue
   Blockage or EJD ~40%



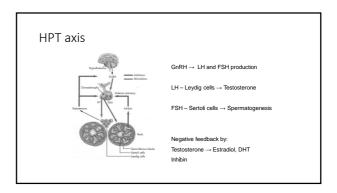
#### Copyright © Oakstone Publishing, LLC, 2018. All Rights Reserved.

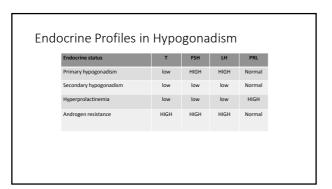


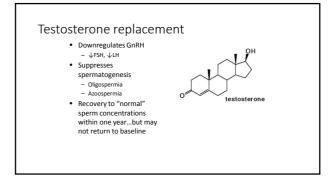


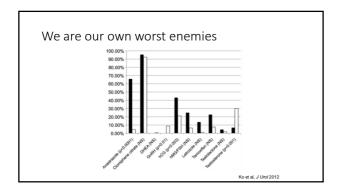
#### **Endocrine Profile**

- Testosterone (AM draw)
- Follicle stimulating hormone
- Luteinizing hormone
- Estradiol
- Prolactin
- Thyroid Stimulating Hormone









#### T optimization: whom to treat?

- T <400 ng/dL
- Sexual dysfunction
- Suboptimal semen parameters
- ?Consider in those with recent history of testosterone/anabolic steroid use

#### T optimization – how to treat?

- \*Clomiphene citrate
- hCG +/- FSH

#### Clomiphene citrate\*

- Blocks estrogen feedback at level of hypothalamus and pituitary
   Increases production of FSH and LH
   Stimulates testicular function
- Dosing:
  - 50 mg every other day
     50 mg TIW
     25 mg daily

\*(off-label use)

Whitten et al. Fertil Steril 2006

#### Aromatase Inhibitors\*

- Blocks conversion of testosterone to estradiol
- Increase in T:estradiol
   May see increase in FSH and LH due to lack of negative feedback by estradiol
- Dosing:
  - Anastrozole 1 mg daily

\*(off-label use)

Raman and Schlegel, J Urol 2002 Roth MY et al. Nat Clin Prac Endocrinol Metab 2008

#### **Gonadotropin Treatment**

- hCG stimulates Leydig cells (same action as LH)
- 1000-3000 U 2-3x weekly
- FSH stimulates Sertoli cells FSH 75-150 U 3x weekly
- hMG (LH+FSH) 75-150 U 2-3x weekly

Liu PY et al. J Clin Endocrinol Metab 2009

#### Hypogonadotrophic hypogonadism (e.g., prior pituitary surgery, Kallmann Syndrome)

- Low FSH
- Low LH
- Low serum T
- [normal PRL]
- [normal pituitary MRI]

Treat with gonadotropins (can consider clomiphene in mild cases)

#### Genetic testing Production-related (azoospermia, severe oligo J() | 1 ) X X Karyotype - Klinefelter syndrome (47XXY) (47XXY) Robertsonian translocations Reciprocal translocations Y microdeletions (long arm) AZFa, AZFb → no sperm AZFc → sperm extraction Obstruction-related (azoospermia/absent vasa) CFTR testing

#### Klinefelter Syndrome

- 1:500-1:1000 live male births
- Majority nonmosaic, fewer mosaic (46XY/47XXY)
- Hallmark: atrophic testes, primary hypogonadism
  - Elevated FSH
  - Low or low-normal serum T

  - Decreased germ cell mass, azoospermia
     Associated with diabetes, learning disabilities, increased risk for breast cancer, non-Hodgkin lymphoma

#### Congenital Bilateral Absence of the Vasa Deferentia

- Accounts of 6% of cases of obstructive azoospermia
  Accounts of 6% of cases of obstructive azoospermia
  Accounts of 6% of cases of obstructive azoospermia
  Accounts of cases of
- Men with CEAND should be offered genetic testing and counseling, as well as their female partners
   Imaging for renal anomalies should be offered in those with unilateral vasal agenesis or CBAVD and no evidence of CFTR abnormalities

Male Reproductive Surgery

#### Surgically-treatable Male Factor Issues

- Obstruction
  - Congenital absence of vasa deferentia

  - latrogenic (e.g., previous hernia repair)
     Prostate utricle/Mullerian duct cyst, SV cysts
- Spermatogenic dysfunction

#### Varicocele incidence

- 15% in general population
- 35% with primary infertility
- 80% with secondary infertility
- L>>R
- 15-50% cases bilateral
- Isolated right varicocele fairly rare



# Varicocele evaluation • Physical examination • Visualization of veins: "bag of worms" • Palpation of veins within spermatic cord • Doppler U/S

#### Varicocele Grading System

Grade	Physical Exam
1	Palpable on exam only w/ Valsalva
2	Palpable on exam without Valsalva
3	Visible on exam

#### Varicocele – intervention

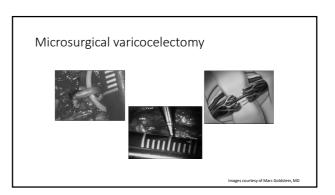
- Male factor infertility
  - Oligospermia, asthenospermia
- Testicular size differential
- (Pain)
- (Consider for low testosterone)
- Adult men with palpable varicocele and normal SA/bloodwork may be followed with periodic testing

#### $\ \ \, \text{Varicocele} - \text{treatment options}$

- Retroperitoneal
- Inguinal or subinguinal varicocelectomy
- Microsurgical varicocelectomy
- Laparoscopic varicocelectomy
- Percutaneous embolization

Type of repair	Pregnancy rate (%)	Recurrence rate (%)	Hydrocele rate (%)
Open (all types) (22)	29	14	0.1
Open (inguinal) (21)	31	11	3
Laparoscopic (22)	30	17	0.08
Open microsurgical (22)	40	2	0 (0.005)
Sclerotherapy (antegrade) (30)	42	11	0
Sclerotherapy (retrograde) (30)	30	11	0

Velasquez and Tanrikut, Transl Androl Urol 2014

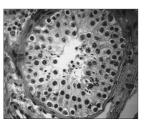


#### Impact on Testicular Function

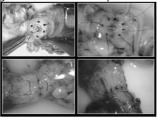
- Significant improvement in semen parameters in 60-80% of men
   Greater improvement associated with larger grade varicocele and poorer starting parameters
- Reported pregnancy rates 30-60%
- Prevention of progressive functional decline
- Cost-effective

- Constailer Curve
  Timpact:
  Combailer and Vermeulen (J Clin Endocrinol Metab, 1975)
  Serum testosterone levels returned to normal after varioccelectomy
  Suet al. (J Ural, 1995)
  Significant improvement in testosterone production post-varioccelectomy
  Tanknuter al. (BJU Int., 2011)
  Significant increase in post-op T levels in more than 2/3rds of patients

#### Obstructive azoospermia



#### Microsurgical vasovasostomy



#### Vasovasostomy outcomes

- Patency rates: 70-95%

  \*\*Length of time since vasectomy

  Presence of sperm intraoperatively in vasal fluid

  - Gross appearance of vasal fluid
     Length of vasal segment
     between epididymis and
     vasectomy site
- Presence of sperm granuloma
- Paternity rates: 30-75%
  - Female partner age is most important determining factor



# Microsurgical vasoepididymostomy

Patency 40-85%

#### Transurethral Resection of Ejaculatory Ducts (TURED)

- Diagnosis of EDO:
  - Low-volume, low-pH (<7.2), fructose-negative azoospermia
  - Dilation seen on TRUS
- SV aspirate +sperm
- Sperm return to ejaculate in 50-75%
- Conception rate ~25%



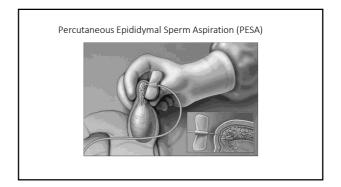
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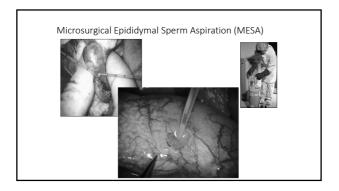
#### Sperm Extraction

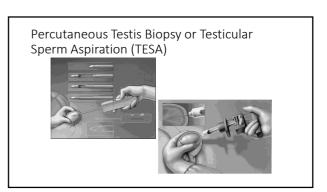
- Epididymis
  - microsurgicalpercutaneous
- percutaneoTestis
- open biopsypercutaneous

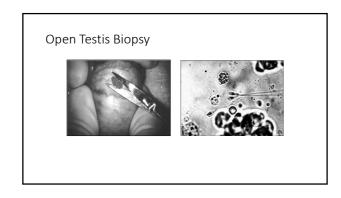
Necessitates IVF-ICSI!!

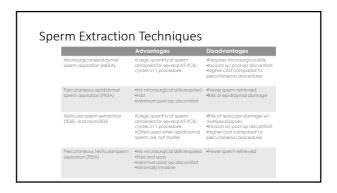




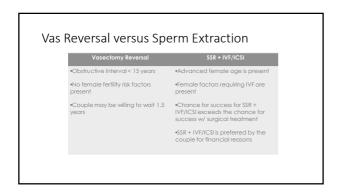


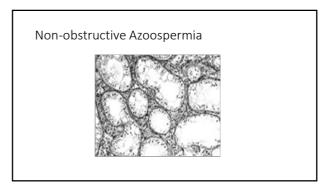


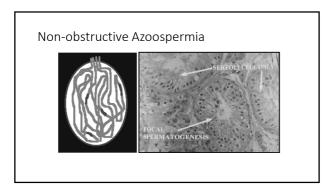


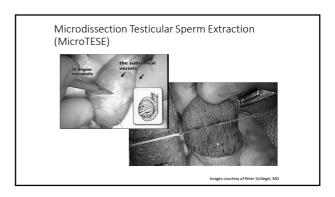


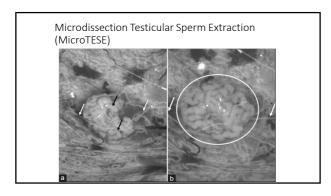
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#### Conclusions

- A good understanding of male reproductive anatomy and physiology is essential to effectively evaluating and treating male fertility patients
- There are medical and surgical treatment options available for most men with male factor infertility
- Female partner age is the most important predictive factor in terms of likelihood of conception
- Important to counsel patients regarding all treatment options as well as the timeline to treatment

#### **Erectile Dysfunction: Exploring Options for Treatment**

Arthur L. Burnett, M.D., M.B.A., F.A.C.S. Professor of Urology The James Buchanan Brady Urological Institute Johns Hopkins Medicine Baltimore, Maryland, U.S.A.

Disclosure Statement: In accordance with ACGME policy on relevant financial disclosure, I disclose financial relationships with the following entities:

Research Grants: Boston Scientific, Astellas **Expert Testimony: Abbvie** 

#### Rise of Sexual Medicine: History Highlights I

- Antiquity
- India, circa 1000 B.C.
- Greece, circa 320 B.C. ■ China, 300 B.C.
- Rome, circa A.D. 50

- Europe, circa 1350
- Europe, circa 1700

- Rhinocerus horn Oysters
- Rock salt
- Ram testicle, boiled in milk
- Satyrion (plant)
- **■** Cloves
- Ginger ointment
- Dried black ants and olive oil Jackal bile ointment Melted fact from camel humps
- Ground-up Spanish fly ointment/ potion

#### Rise of Sexual Medicine: History Highlights II

- Early to mid-1900's
- 1936
- 1952
- 1954
- 1967
- ointment
- Rotten leeches ointment

- **1912**

- 1973 **1983**

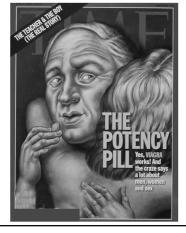
**1998** 

- 1995 ■ 1996

- Psychoanalysis (Sigmund Freud)
- Yohimbine
- Cartilage implant (Bogoras)
- Acrylic splint implant
- Sex-therapy (Masters & Johnson)
- Vacuum-pump technology ■ Penile revascularization (Michal)
- **■** Intracavernous pharmacotherapy (Brindley/Virag)
- Caverject (alprostadil)
- Intraurethral alprostadil ■ PDE5 inhibitor therapy



- **■**Management principles
- **■**Diagnostic evaluation
- **■**Treatment considerations



# The Male Sexual Response and Associated Disorders | Comparison | Comp

#### **Management Principles**

- Acknowledgment of the subjective complaint of erectile inability by the patient (or patient and partner)
- Structured process that incorporates social clinical practice concepts to bring patients the best therapeutic outcomes

#### **Clinical Practice Concepts**

- Early detection
- Shared decision-making and treatment planning
- Role of partner interview
- Cardiac risk assessment
- **■** Follow-up care

#### **Detection**

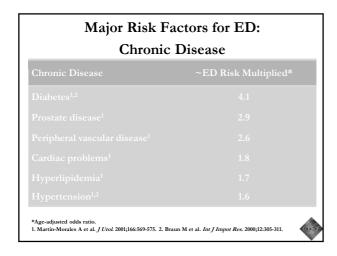
- Risk factor identification
- Screening high risk populations
- **■** Diagnostic questionnaires

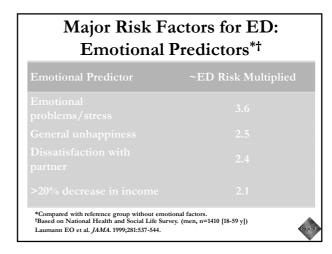
#### Use of Validated Questionnaires

For the man with ED, validated questionnaires are recommended to assess the severity of ED, to measure treatment effectiveness, and to guide future management. (Expert Opinion)

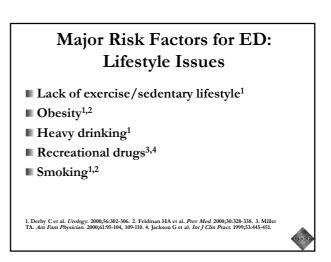
- eg, International Index of Erectile Function (IIEF),
   Erection Hardness (EHS), Sexual Health Inventory for Men (SHIM)
- Not valid for sexually inactive men

# Organic Causes of ED: Percentage Distribution 40% Vascular 30% Diabetes 1% Other 15% Medication 3% Endocrine 5% Neurological 6% Pelvic surgery, radiation, or trauma With permission from Goldstein I, and the Working Group for the Study of Central Mechanisms in Erectile Dysfunction. Sci Am. August 2000;70-75.





# Major Risk Factors for ED: Emotional Predictors\* Emotional Predictor ~ED Risk Multiplied Pessimistic attitude 3.9† Depression 2.9† Negative outlook on life 2.3† Marital change 1.4 Employment change 1.4 \*Based on the Massachusetts Male Aging Study. (N=1265) \*PP-0.5. Reprinted from Urologic Clinics of North America, Volume 28, Rosen RC, Psychogenic erectile dysfunction: classification and management, pages 269-278, copyright 2001, with permission from Elsevier Science.



#### **Shared Decision-Making**

- $\blacksquare$  SDM is the cornerstone of patient-centered care
  - Sharing of information between patient and clinician is critical
- Clinician needs to be aware of
  - Health literacy of patient
  - Social, cultural, religious factors
- Panel strongly recommends involving a man's partner where possible and appropriate

Elwyn 2012, Enstein 2004, Hoffmann 2015, Hatzichristou 2010, Vemulakonda 200

#### Importance of Partner Interview\*

- Partner interview shown to impact diagnosis and treatment 58% of the time<sup>1,2</sup>
- Partner can provide important information<sup>1-3</sup>
  - New perspective on sexual issues
  - Insight into quality of the relationship
  - Role in sexual dysfunction

\*Partner interview may require a second visit.

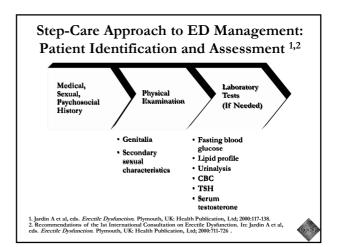
1. Tiefer I., Schuetz-Mueller D. Urol Clin North Am. 1995;22:767-773. 2. Chun J, Carson CC III. Urol Clin North Am. 2019;28:495–3. 3. Tiefer I., Melman A. Sev Disabil. 1983;6:167-175.

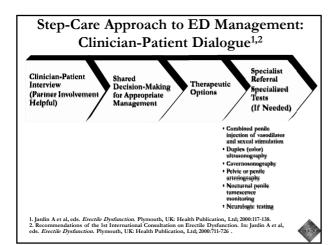


#### Cardiac Risk Assessment

- Recognition of the coexistence of ED and cardiovascular disease
  - Epidemiologic studies
  - Basic science research
- All ED patients require stratification of cardiovascular risk
  - High risk patients of unstable or refractory angina, recent history of myocardial infarction, certain arrhythmias, uncontrolled hypertension, should undergo cardiologic referral for cardiovascular stress testing and risk reduction therapy
  - Even low risk patients should receive minimum recommendations of cardiovascular disease management, e.g., lifestyle modifications, regular health monitoring

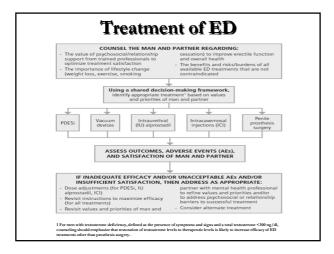
Kostis JB et al. Am J Cardiol 2005; 96:85M-93M.





#### **Specialist Referral Indications**

- Failure of initial treatment
- Younger patients with a history of pelvic or perineal trauma
- Patients with significant penile deformity
- **■** Complicated endocrinopathies
- Complicated psychiatric or psychosexual disorders
- Need for vascular or neurosurgical intervention
- **■** Medicolegal reasons



#### Role of Mental Health Professional

For men being treated for ED, referral to a mental health professional should be considered to promote treatment adherence, reduce performance anxiety, and integrate treatments into a sexual relationship. (Moderate Recommendation; Evidence Level: Grade C)

- ED occurs in complex psychosocial context related to masculinity and sexuality
- Psychotherapy or psychosexual counseling may be helpful

### Lifestyle Modifications for Comorbid Conditions

Clinicians should counsel men with ED who have comorbidities known to negatively affect erectile function that lifestyle modifications, including changes in diet and increased physical activity, improve overall health and may improve erectile function. (Moderate Recommendation; Evidence Level: Grade C)

- Metabolic conditions
- Cardiovascular conditions

#### PDE5i Availability

Men with ED should be informed regarding the treatment option of an FDA-approved oral phosphodiesterase type 5 inhibitor (PDE5i), including discussion of benefits and risks/burdens, unless contraindicated. (Strong Recommendation; Evidence Level: Grade B)

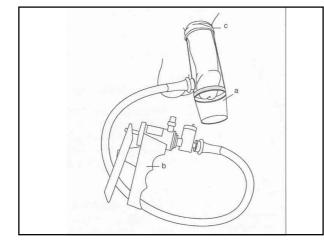
- In the US: sildenafil, tadalafil, vardenafil, and avanafil
- Effective in about 60% of men

#### Oral Pharmacotherapy: Type V PDE Inhibitors

- Mechanism of Action
  - "Augments" corporal smooth muscle relaxant effects
- Dosage/Administration
  - Lead time for gastrointestinal absorption
  - Presence of sexual stimulation
- Efficacy
  - 70% successful sexual intercourse rates
- Side Effects
  - Headaches, flushing, dyspepsia, nasal congestion, visual disturbances
- Contraindications
  - Nitrate therapy in any form
  - Alpha-blocker considerations

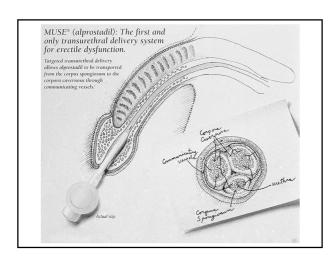
#### **Vacuum Constriction Devices**

- **■** Mechanism
  - Negative pressure mechanically produces penile blood filling
- Dosage/Administration
  - Technical requirements
- **■** Efficacy
  - Erection-like state: 67-90%
  - Satisfaction rates: 34-68%
- Side Effects (minor)
  - Genital ecchymosis, penile "pivoting"/coldness
- Contraindications
  - Sickle cell disease



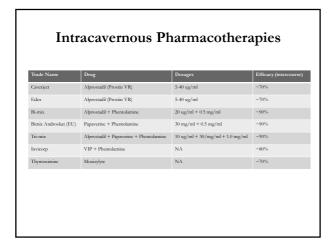
# Intraurethral Pharmacotherapy: MUSE (Alprostadil)

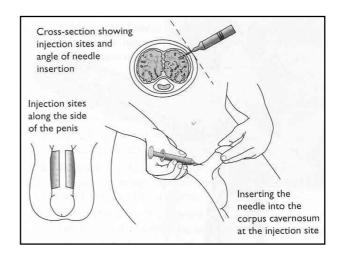
- **■** Mechanism of Action
  - Induces" corporal smooth muscle relaxant effects
- Dosage/Administration
  - Technical requirements
  - Proper dosing titration
- Efficacy
  - Responder rate: ~50%
- Side Effects
  - Local pain, urethral bleeding, dizziness, hypotension
- **■** Contraindications
  - Men with priapism histories



#### Intracavernous Pharmacotherapy

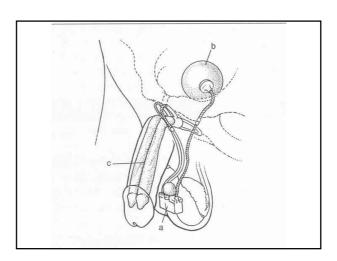
- **■** Mechanism of Action
  - "Induces" corporal smooth muscle relaxant effects
- Dosage/Administration
  - Technical requirements
  - Proper dosing titration
- Side Effects
  - Penile pain, penile fibrosis, priapism
- **■** Contraindications
  - Men with priapism or severe coagulopathy histories





#### Penile Prosthesis Surgery

- **■** Indications
  - Major penile injury or deformity
  - When medical therapy is contraindicated, unsuccessful, or undesirable
- **■** Mechanism of Action
  - "Splint" within the penis produces rigidity
- **■** Technique
  - Hand dexterity
- Side Effects
  - Risk of infection or device malfunction
- **■** Contraindications
  - Surgical candidacy considerations



#### Penile Vascular Surgery

- Arterial Revascularization
  - Considered to address arteriogenic ED
  - Indications: age less than 55 years, non-smoker, non-diabetic, absence of venous leakage, radiographic confirmation of stenosis of the internal pudendal artery
  - Options: inferior epigastric artery input to dorsal artery or vein
- **■** Venous Reconstruction
  - Proposed to correct veno-occlusive ED
  - Presently considered investigational
    - Owing to inaccurate or deficient methods for diagnosing and correcting the relevant defect

#### Follow-Up Issues

- Reassessment of medical and psychosocial conditions
- Evaluation of potential adverse drug reactions or drug interaction effects
- Evaluation of the need for dosage titration or treatment substitution
- Attention to patient responses to therapy and satisfaction

# Expected Developments in the Near Future

- New pharmacologics
  - Guided by pathophysiology
- New surgery techniques
  - Tissue transplants
- New devices

#### **Key Points**

- Approximately 20% of adult men worldwide experience ED.
- The basic evaluation of ED consists of a detailed case history, physical examination, and proper laboratory tests.
- An informed decision-making process that combines goals and preferences of the patient (and partner) and balanced and thorough guidance of the clinician should dictate the best therapeutic outcome.

#### **Comprehensive Review** of Urology:

#### Peyronie's Disease and Priapism

Hossein Sadeghi-Nejad, MD, FACS

Professor of Surgery in Urology Rutgers- New Jersey Medical School Hackensack University Medical Center Chief of Urology, VA NJ Health Care System



CrossMark

# **Financial Disclosures** None RUTGERS

#### Peyronie's Disease

American Urological Association (AUA) Guideline

#### PEYRONIE'S DISEASE: AUA GUIDELINE

Ajay Nehra, Ralph Alterowitz, Daniel J. Culkin, Martha M. Faraday, Lawrence S. Hakim, Joel J. Heidelbaugh, Mohit Khera, Kevin T. McVary, Martin M. Miner, Christian J. Nelson, Hossein Sadeghi-Nejad, Allen D. Seftel, Alan W. Shindel, and Arthur L. Burnett

SEXUAL MEDICINE

Evidence-Based Management Guidelines on Peyronie's Disease

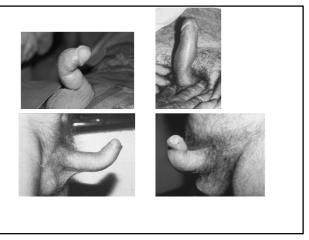
Eric Chung, FRACS,<sup>3,2</sup> David Rajah, FRCS,<sup>3</sup> Ates Kagioglu, MD,<sup>4</sup> Cullio Garaffa, FRCS,<sup>3</sup> Ahmed Shamsodini, MD,<sup>5</sup> Tiririty Bivalacqua, MD,<sup>6</sup> Sidney Clina, MD,<sup>7</sup> Lawrence Hakim, MD,<sup>8</sup> Hossein Sadeghi-Nejad, MD,<sup>9</sup> and Gregory Broderick, MD,<sup>9</sup>

#### PEYRONIE'S DISEASE DEFINITION

...An acquired penile abnormality characterized by fibrosis of the tunica albuginea, which may be accompanied by pain, deformity, erectile dysfunction, and/or distress...

Appy Nehres, Ralph Alterpoints, Daniel J. Culton, Martha M. Faraday, Lawrence Hallon, Joel J. Holdelbaugh, Mohilt Khera, Kevin T. McVarry, Martin M. Hon Christian J. Nelson, Hossen Sadeghi-Rejad, Afen D. Seftel, Alan III. Shindel, a

HackensackUMC



#### **EPIDEMIOLOGY**

Schwarzer (2001; BJU) community-based; Cologne, Germany

- ➤ Prevalence 3.2% in men aged 31-78 years
- > 7.1% among men aged 50-69 years

El-Sakka (2006 Eur Ur):

> Prevalence 7.9% among men with ED

### Prevalence of Peyronie's Disease: 8,000-Man Survey

#### Clinical complaints:

- Angulation
 - Painful erections
 - Erectile dysfunction
 - Combination
 119/142 (84%)
 (46%)
 (46%)
 (40.8%)
 (40.8%)
 (40.4432)
 (1.03%)

U. Schwarzer et al., J Urol 2000

#### **PATHOPHYSIOLOGY**

- Acquired inflammatory disorder of the tunica albuginea
- Microvascular trauma to the penile shaft associated with penile buckling in the erect or semi-erect state secondary to sexual activity
- Many patients do not recall an incident that preceded symptom onset

#### **SYMPTOMS**

- Disorganized, excessive deposition of collagen → formation of plaque within the penile tunica albuginea
- → penile curvature, deformity, and pain
- Erectile dysfunction common
- Emotional and psychosocial consequences are significant

## ACTIVE VS STABLE DISEASE

> Treatment depends on active vs. stable symptoms

Active disease- dynamic and changing symptoms

Penile and/or glanular pain discomfort with or without erection

Stable disease- Symptoms unchanged for at least three months

- Pain with or without erection may be present (less common)
- Curvature may be uniplanar or biplanar and may not be dependent on the size and magnitude of the plaque

#### Natural History Peyronie's Disease

- 12% improve
- 40% remain stable
- 48% worsen

Mulhall et al, J Urol 2006; 175: 2115

Typical active phase 12-18 mo

Significant number will progress

#### **GUIDELINE STATEMENT 5**

The clinician may offer oral non-steroidal antiinflammatory medications to the patient suffering from active Peyronie's disease who is in need of pain management (Expert Opinion)

#### **GUIDELINE STATEMENT 6**

Clinicians should not offer oral therapy with vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine.

[Moderate Recommendation; Evidence Strength Grade B(vitamin E)/ B( omega-3 fatty acids)/ B (Vitamin E + propionyl-Lcarnitine)/C(tamoxifen)/ C(procarbazine)]

#### **GUIDELINE STATEMENT 7**

Clinicians should not offer electromotive therapy with verapamil. (Moderate Recommendation; Evidence Strength Grade C)

#### **GUIDELINE STATEMENT 8**

Clinicians may administer intralesional collagenase clostridium histolyticum combination with modeling by the clinician and by the patient for the reduction of penile curvature in patients with stable Peyronie's disease, penile curvature >30° and <90°, and intact erectile function (with or without the use of medications). (Moderate Recommendation; Evidence Strength Grade B)

Clinical Efficacy, Safety and Tolerability of Collagenase Clostridium Histolyticum for the Treatment of Peyronie Disease in 2 Large Double-Blind, Randomized, Placebo Controlled Phase 3 Studies

Martin Gelbard,\*,† Irwin Goldstein,‡ Wayne J. G. Hellstrom,§ Chris G. McMahon,‡ -Ted Smith,‡ James Tursi,‡ Nigel Jones,‡ Gregory J. Kaufman‡ and Culley C. Carson III‡

- Two Multicenter Randomized, Double Blind, Placebo Controlled Studies
- USA and Australia (IMPRESS I & II)
- Primary end points
  - Improvement (%) from baseline penile curvature
  - Change from baseline in PD symptom **bother** (PDQ)

JOURNAL OF UROLOGY® Vol. 190, 199-207, July 2013

## IMPRESS I and II – Intralesional Collagenase Plus Modeling

- The definitive trials that lead to FDA approval
- Up to 8 injections of 10,000 U over 24 weeks
- Clinician modeled the penis after each cycle
- Patients were instructed to model at home 3 x day
- Follow up 7.5 months
- Exclusion criteria more extensive than 2012 trial:
  - Curvature <30° or >90°
  - Isolated hourglass deformity without curvature
  - Calcified plaque or curvature proximal to base
  - ED unresponsive to PDE5 inhibitors
  - Lack of PGE1 erection during measurement

## IMPRESS I and II- Intralesional Collagenase Plus Modeling

Subgroup	Change from baseline curvature	% change from baseline curvature
Collagenase + modeling (n=202)	-17.0°	33% reduction
Placebo + modeling (n=107)	-9.30	18.2% reduction

#### Co-primary endpoint result Erectile curvature improvement from baseline to week 52



33% change from baseline represented in the images



### **GUIDELINE STATEMENT 8 Considerations**

Body of evidence strength is Grade B

Expected average curvature reduction is 17 degrees

Average <u>difference between collagenase and</u> placebo was statistically significant but only 7.7°

IIEF overall satisfaction improvement by one point

#### BJU Sexual Medicine

Analysis of the clinical safety of intralesional injection of collagenase *Clostridium histolyticum* (CCH) for adults with Peyronie's disease (PD)

Culley C. Carson III, Hossein Sadeghi-Nejad\*, James P. Tursi<sup>†</sup>, Ted M. Smith<sup>†</sup>, Gregory J. Kaufman<sup>†</sup>, Kimberly Gilbert<sup>†</sup> and Stanton C. Honig<sup>‡</sup>

BJU Int 2015; 116: 815-822

#### **GUIDELINE STATEMENT 9**

Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional collagenase regarding potential occurrence of adverse events, including penile ecchymosis, swelling, pain, and corporal rupture. (Clinical Principle)

#### **GUIDELINE STATEMENT 10**

Clinicians may administer intralesional interferon  $\alpha$ -2b to patients with Peyronie's disease. (Moderate Recommendation; Evidence Strength Grade C)

#### Injection Technique

Local (over injection site) or penile nerve block

- Multiple punctures (25-27 g. needle) into the plaque → widely distribute drug
- 6-10 cc of mixed solution per session q 2 wks: 6-12 plaque injections total







# Intralesional Interferon $\alpha$ -2b Trial

- Evaluated the use of intralesional IFN  $\alpha$ -2b
- Average PD symptoms >12mo
- 5 MU of IFN α-2b q 2 weeks for 12 weeks (Note: many studies use 2MU in 10cc)
- Curvature, plaque size, penile pain, erectile function and penile hemodynamics were measured at baseline and study completion
- Inclusion criteria
- Curvature >30°
- Exclusion criteria
  - Calcified plaques

#### Interferon α-2b

	Subgroup	Change from baseline curvature	with	Decrease in size of plaque
	IFN a-2b (n=50)	-13.50	67.7%	2.6 cm <sup>2</sup>
l	Placebo (n=53)	- 4.50	28.1%	0.9 cm <sup>2</sup>
П	IEN . O			

IFN  $\alpha$ -2b: significant improvement in outcomes except EF Significant improvement in PSV and mean resistive index

- Proportion of men with normal vascular status increased significantly in IFN group (31.5% to 57.8%) but not in placebo
- > 9º difference vs placebo

#### Interferon α-2b Considerations for Patient Counseling

Body of evidence strength is Grade C. Expected average curvature reduction: 13.5° Average difference with placebo: 9 degrees

Despite modest curvature reduction, consider reduction in other PD outcomes (plaque size, pain, vascular outcome)

## **GUIDELINE STATEMENT**11

Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional interferon  $\alpha$ -2b about potential adverse events, including sinusitis, flu-like symptoms, and minor penile swelling. (Clinical Principle)

40-100% with AEs. Effectively managed with OTC NSAIDS; Duration of AEs typically 48 hours or less

#### **GUIDELINE STATEMENT 12**

Clinicians may offer intralesional verapamil for the treatment of patients with Peyronie's disease. (Conditional Recommendation; Evidence Strength Grade C)

Note: Dose is typically 10 mg / 10 cc

# Randomized Controlled Trials: Intralesional Verapamil

#### **Rehman Trial**

- Mean disease duration of 16 months
- Baseline mean curvature of 37.7° in verapamil group, 33.6° in placebo 10-27 mg administered weekly for 6 months
- Reported significant decrease in plaque length, width, and volume in verapamil group but not in the placebo group

#### Shirazi Trial

- Mean disease duration of 21.3 months
- Baseline mean curvature of 49.7º in verapamil group, 45.6º in placebo
- 10 mg administered twice weekly for 3 months
- Reported similar decrease in plaque length, width, and volume in both groups

#### **Intralesional Verapamil**

- ➤ Body of evidence strength is Grade C based on conflicting findings from the RCT trials.
- ➤ Lack of control for natural PD course increases the uncertainty of the results
- ➤ Clinicians should be aware that the balance between benefits and risks is unclear.

Cost considerations not addressed by the AUA panel Potential advantage for some patients

#### **Verapamil Adverse Events**

Penile bruising, dizziness, nausea, and pain at the injection site.

Generally very mild in nature

#### **Shock Wave Therapy**

Do <u>not</u> use for the reduction of penile curvature or plaque size.

ESWT may be used to improve penile pain

(AUA-G Conditional Recommendation; Evidence Strength Grade B)



#### **Surgical Approaches**

- Tunical Shortening Procedure Reconstructive procedures on convex side (opposite to the plaque)
- Penile Lengthening Procedure Reconstructive procedure on concave side (same side as plaque) - incision/excision & grafting
- Penile Prosthesis (manual modeling, tunical incision/excision <u>+</u> grafting)

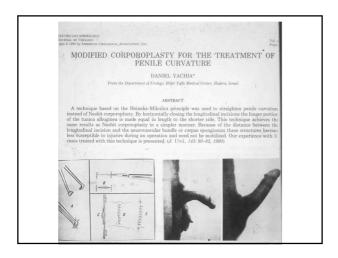
### Tunical Shortening Procedures

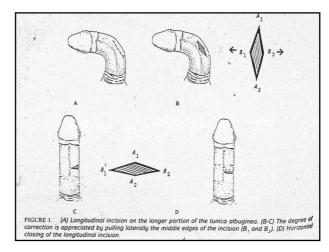
Nesbit Procedure (1965) – initially described for correction of congenital abnormalities of penis

- Pryor (1985) applied technique to Peyronie's deformities
- Technique circumcision incision, artificial erection, ellipse(s) excised – 1 mm for every 10° curvature
- Results simple, safe, 80% success rate
- Drawbacks Penile shortening (13-37%), urethral injury, glans numbness, hematoma, ED

### Tunical Shortening Procedures

- Modified Nesbit Procedure (Lemberger 1984, Yachia 1990)
- Allis clamps used to straighten penis with artificial erection, longitudinal incision, closed horizontally (Heineke-Milkulicz principle)
- Results 90% successful straightening, 95% preservation of erections, 80% satisfaction
- Drawback Penile shortening in 67%

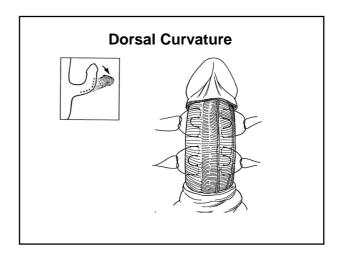


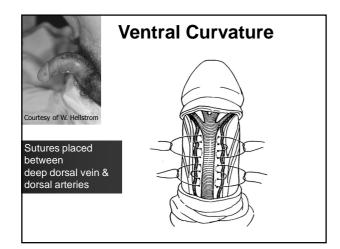


# **Tunical Shortening Procedures**

#### **Plication Procedures**

- No excision or incision
- Non-absorbable sutures (2-0 Ticron, Prolene, Tevdek) placed on opposite side to curvature and knots buried
- -2-3 pairs of sutures usually used
- Results: Success 40-100%
- Drawbacks Recurrence of curvature, penile pain and shortening





### Tunical Lengthening Procedures

- Indications: Severe curvatures, marked penile shortening (or short penis), deformation, or waisting
- Incision/excision of plaque and graft placement
- Drawbacks Sensory deficit, urethral injury, residual /recurrent curvature, <u>ED</u>

#### **Grafting Materials**

- Autografts
  - e.g.: dermis, dura mater, tunica vaginalis, dorsal penile or saphenous vein, temporalis fascia, crura, fascia lata, etc.
- Synthetic Inert Substances

> e.g.: Dacron, Gortex, silicone with silastic borders

Allografts or Xenografts

>Human cadaveric pericardium (ie Tutoplast, Coloplast, Denmark) SIS (porcine small intestinal submucosa) (Cook, Indianapolis, IN)

#### **Excision and Grafting**

- Buck's fascia entered just <u>lateral to the</u>
- Dissect the neurovascular bundle free for dorsal plagues and the urethra for ventral plaques.
- Alternatively, dorsal approach by removing the dorsal vein and dissecting neurovascular bundle off laterally to expose plaque

#### **Incision/Partial Excision** & Grafting - Indications

- Surgical Algorithms & Guidelines agree x 20y
- Must have strong pre-op erections !!!
- Curvature > 60 degrees
- Significant shaft narrowing
- Hinge-effect present
- Extensive plaque calcification

N.B. - Plaque and deformity stable & coitus compromised 2° deformity

Ralph et al JSM 2010;

#### Advantages of PIG/PEG **Procedure**

- Best opportunity to correct severe curvature > 60-70°
- Only approach to reestablish girth & correct hinge
- Least likely to cause further length loss
- Most likely to enhance length with or without traction post-op

#### Severe Curve 85° w/ Indent and Hinge



Courtesy of L. Levine, M.D.

#### Caliber & Curve Corrected



Courtesy of L. Levine, M.D.

#### **Complications of Grafting**

- Hematoma
- Wound infection
- Urinary retention or urethral injury
- Distal sensory deficit/numbness of glans (neuropraxia)
- Diminished distal rigidity (venous leak ?)
- Graft contraction
- Erectile dysfunction

#### Inflatable Penile Prosthesis

Indications: PD & ED

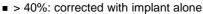
- Malleable: poor long-term satisfaction (Montorsi, J Urol 1993)
  Inflatable: (AMS-CX or Coloplast Titan best;
  Never AMS-Ultrex; LGX NOT recommended)
- Possible AEs
   – infection, urethral injury, distal sensory deficit, prosthesis failure, penile shortening

Wilson SK, Delk JR: J Urol 152:1121, 1994 Montague DK et al: J Urol 156:1633, 1996

#### Patient with curvature > 70°







- 30° or less → no adjunctive measures
- Hourglass deformity: corrects with time
- Inflated cylinders act as a tissue expander
- With usage after 1 yr → straight & symmetrical





Protect pump with clamps

Protect corporotomies

Insert & inflate IPP to maximum
Bend penis in opposite direction <u>firmly</u>
Hold pressure for 90 seconds
Remove clamps & inflate again ( 2 or 3 pumps)

Wilson, Delk: J Urol 165:825, 2001

#### **Modeling Procedure**







Reprotect & repeat modeling
After 2 modeling sessions, deflate completely
Pull on strings & only inflate 75%
Then judge results — quit if <30°

#### **IPP + Modeling Procedure**

Urethral Injury: 4%Corporal Rupture: 2%

AMS CX or Coloplast Titan

■ AMS LGX not recommended

Wilson SK, Delk JR: J Urol 152:1121, 1994 Montague DK et al: J Urol 156:1633, 1996

#### Take Home Messages Medical Therapies

- > ~ 5% of the population affected
- > Heterogeneous presentation
- > Individualized Treatment
  - > Review of AEs, costs, comorbidities
- ➤ Modeling is critical in collagenase Rx
- Not optimal for patients with PD and ED unresponsive to PDE5-Is

#### Take Home Messages Surgical Therapies

- ➤ Many will need surgery
- Gold standard for definitive correction
- Penile plication procedures are generally safe with an easier learning curve
- Provide excellent results (92-99% curve improvement or resolution) with minimal morbidity
- Excision grafting considered for severe cases
- IPP and modeling for PD + ED combination



#### **Priapism Update**

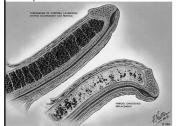
Hossein Sadeghi-Nejad, MD, FACS

Professor of Surgery in Urology Rutgers— New Jersey Medical School Hackensack University Medical Center Chief of Urology, VA NJ Health Care System



#### **Priapism Definition:**

Pathological condition of a penile erection - persists beyond or unrelated to sexual interest or stimulation



4 hours

Sadeghi-Nejad H and Seftel A Current Urology Reports 2002, 3:492-49

AFUD Thought Leader Panel, IJIR 5:S39, 2001

#### Classification

- Ischemic
  - Veno-occlusive or low flow. Nonsexual persistent erection with little or no cavernous blood flow. Corpora is rigid and tender to touch
- Non-ischemic
  - Arterial or high flow. Nonsexual persistent erection with unregulated cavernous arterial inflow. Phallus is neither fully rigid nor painful
- Stuttering
  - Ischemic priapism with intervening periods of detumescence

#### Classification

- Ischemic (veno-occlusive" or "low flow")
   Most common variant (~ 95% of cases)
  - · Trapping of mixed venous blood
  - ischemia & pressure → pain & rigidity
- > Very high ED rates (~ 90%) if > 24 hrs

#### TRUE EMERGENCY

Pryor, J. and Hehir, M. (1982) Br J Urol

#### Classification

- > Non-ischemic ("high flow" or "arterial")
  - Elevated vascular flow through corpora Penile/perineal trauma
  - Corpora cavernosa not fully rigid or painful
  - No hypoxia / acidosis on blood gas sampling

# High Flow Priapism - Etiology Table 2 Etiology of the 202 cases of high-flow priapism reported in the literature.<sup>a</sup> Etiology Percentage of cases Traumatic/latrogenic laceration of a penile artery 70.5 Blunt penile trauma 3.8 Blunt penile trauma 40.4 Straddle trauma 2.4.4 Cavernosography 0.6 Penile revascularization 1.3 Malignant arrosion of penile vessels 4.5 Inherited disease (sickle cell anemia, FARRY'S DISEASE) 5.8 Drug abuse and intracavernous injection of prostaglandin E1 2.5 Unknown 16.7 \*Table compiled using data presented by Kuefer and associates.<sup>2</sup> Bochinski DJ et al. (2004) Erectile dysfunction and priapism. Nat Clin Pract Urol 1: 49-53 doi:0.1038/ncpuroocc2

# Classification Other categories

- Recurrent (Stuttering) Priapism
   Recurring ischemic attacks, often sickle cell patients
- Refractory Priapism

Immediately recurrent nonischemic erectile state following aspiration/incision of the corpora for ischemic priapism Veno-occlusive priapism can convert to non-ischemic priapism

- Neurogenic Priapism
   Central/Peripheral nervous dysregulation
- Idiopathic
- Drug Induced

#### **Epidemiology**

- ➤ 1.5 per 100,000 person years •2.9 if > 40 years old
- ➤ Much higher in "at risk" population
- > 42% 64% prevalence in SCD
- ➤ Sickle β-Thal → 89% probability age 20

Eland et al; Urology, 2001, 57 (5): 970-2 Mantadakis ey al.; J Ped Hemat Onc, 1999; 21: 518-22

#### Incidence of Priapism in Emergency Departments in the United States

Florian Roghmann,\*,†,‡ Andreas Becker,†,‡ Jesse D. Sammon,† Miriam Ouerghi,† Maxine Sun,† Shyam Sukumar,† Orchidee Djahangirian,† Kevin C. Zorn,§ Khurshid R. Ghani,† Giorgio Gandaglia,† Mani Menon,† Pierre Karakiewicz,† Joachim Noldus† and Quoc-Dien Trinh†

THE JOURNAL OF UROLOGY®
© 2013 by American Linds orders Association Folication and Research, in

- > 5.34 per 100,000 males per year
- > 31.4% increase in summer months
- ➤ 13.3% result in hospitalization
- ➤ Predictors of admission: comorbidity profile, insurance, hospital location, emergency dept volume

#### **Natural History**

- Ischemic Priapism
  - Pryor 2004- reported 90% of men with ischemic priapism lasting 24 hours fail to regain ability to perform sexual intercourse
  - Montague 2003- ED rate of 35% in pts treated systemically with no direct relief of ischemia
- Non-ischemic Priapism
  - Generally have preservation of erectile function
  - 62% spontaneously resolve

# Pathophysiology - Ischemic

- Irreversible effects combination of hypoxia, acidosis and glucopenia at 4 hours
- Reperfusion injury after ischemic priapism resolution
- 12 hours- Trabecular interstitial edema
- 24 hours- sinusoidal endothelium is denuded
- 48 hours- smooth muscle cells undergo necrosis or become transformed into fibroblast like cells

#### Pathophysiology - Nonischemic

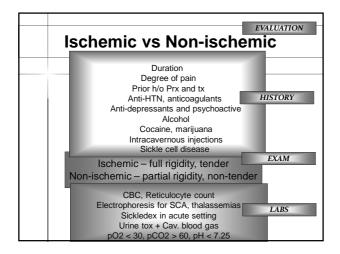
- ➤ Traumatic disruption of penile vasculature → unregulated blood entry
- ➤ <u>Fistula formation</u> between cavernous artery and lacunar spaces → blood bypasses the helicine arteriolar bed

#### **Diagnosis**

- > Unique / "obvious" presentation
- H&P Differentiating factors Pain? Duration? Glans involved? Antecedent factors? Prior episodes/successful Rx? Predisposing conditions? Sickle crisis in SCD?



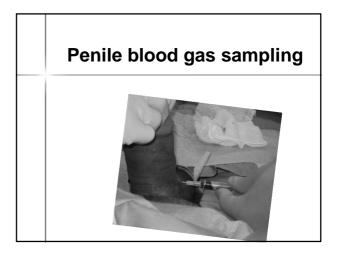
Lab tests should not delay prompt Rx



#### **Diagnosis**

- ■CBC / wbc diff, Plt, urine toxicology, Reticulocyte count & hgb electrophoresis (SCD trait & hemoglobinopathies)
- ■Direct aspiration of corporal blood

# Typical Blood Gas Values Source PO2 (mmHg) PCO2 (mmHg) pH Ischemic priapism < 30</td> > 60 < 7.25</td> Normal ABG > 90 < 40</td> 7.40 Normal Mixed VBG 40 50 7.35



#### Diagnosis: Radiologic Evaluation

Color Doppler Ultrasound
Lithotomy or frog-leg position

- Ischemic: minimal to absent flow in cavernosal arteries / within corpora
- Nonischemic: normal to high flowFistula; Pseudoaneurysm

MRI: Unusual pathologies. Diagnose nonviable tissue. (access, cost, delay)

#### **Treatment Goals**

- >Detumescence
- > Preservation of erectile function
- > Diagnosis of etiology

# Treatment Ischemic Priapism

- > Stepwise + timely / aggressive
  - nerve block
- Aspiration
- > Irrigation when necessary
- > Injection of alpha agents

# Treatment of Ischemic Priapism > Concurrently treat the underlying disease and emergent condition > Treatment proceeds in a stepwise fashion > Surgical shunts should be considered only after injection treatment has failed > Intercavernosal injection of phenylephrine rarely successful if priapism present for > 48hrs No fixed set of rules or a definition of legal standard of care All Quidelines on Prapam. 2003

### Penile aspiration and Irrigation

18 gauge proximal needle insertion

Transglanular angiocath aspiration also an option



## Treatment – Ischemic Priapism

- Corporal aspiration relieves the compartment syndrome
- Counteracts local acidotic and anoxic metabolic derangements

Bivalacqua and Burnett, Urology 2006

- Sympathomimetic agent
  - Better resolution of priapism; less ED

AUA Guidelines, Montague et al. J Urol, 2003

#### **Sympathomimetic Agents**

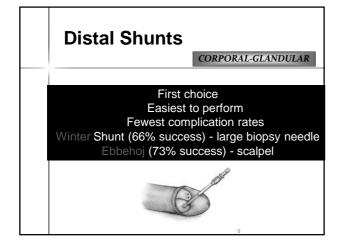
#### **Phenylephrine**

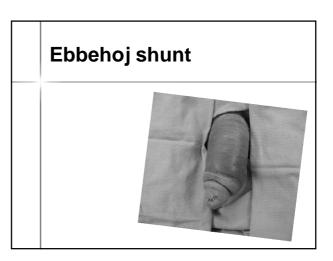
- –Preferred agent based on selectivity (no signif. β effect)
- $-\alpha 1$  agonist.
- $-100-200 \mu q 5-10 min$
- Monitor BP

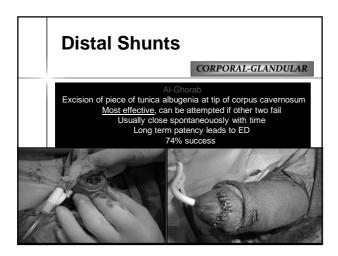
#### **Ischemic Priapism Rx**

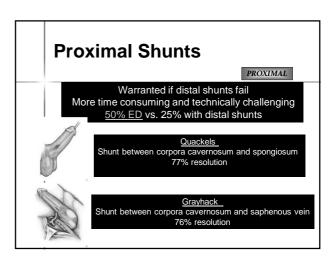
- Repeated aspirations & phenylephrine injections as needed
- Should be done before operating
- 48-72 hours: unlikely to resolve with intracavernous treatment

May require surgical shunting









## Treatment Non-Ischemic Priapism



- >Different approach altogether
- > Initial Rx is OBSERVATION!
- > Aspiration is only diagnostic

# Treatment of Non-ischemic Priapism Nobservation Initial Management Observation Ice and site-specific compression Immediate embolization can be performed - should be counseled re. risk of ED Chance of spontaneous resolution Lack of significant consequences expected from delaying Corporal aspiration is of diagnostic value only Secondary Management Second line tx for failed observation Fig. 78% success and 38% ED with permanent agents Fig. 74% success & 5% ED with temporary embolization (Autologous clot and absorbable gels)

## **Treatment Non-Ischemic Priapism**

#### Embolization possible AEs:

- ED (up to 50%)
- Penile gangrene
- gluteal ischemia
- Purulent cavernositis
- Perineal abscess

# **Treatment Non-Ischemic Priapism**

- Androgen blockade
  - Luprolide, Ketoconazole, Bicalutamide
- Small study (n=7)
- > AEs (decreased libido, fatigue)
- 6 out of 7 improved
- ? Natural progression vs Rx

Mwamukonda, K. Et al., (2010) J Sex Med

#### **Recurrent Priapism**

- RIP or "stuttering"
- Uncommon; Often sleep related
- Typically less than 3-4 hours
- 28% progress to ischemic priapism
- Possible progression to corporal fibrosis and ED

Morrison BF and Burnett AL, Curr Urol Report; 2012 Montague et al, AUA Guidelines, J Urol 2003

#### **Recurrent Priapism**

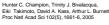
- SCD most common cause
  - 72% with priapism have RIP episodes
- Idiopathic and neurological causes
- History of prolonged (> 4 hr) priapism episode may predispose to RIP

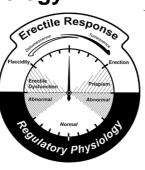
Adeyoju et al; BJU Int 2002; 90: 898-902 Broderick and Harkaway; IJIR; 1994; 6: 9-16

# Recurrent Priapism Pathophysiology

Phosphodiesterase -5A dysregulation in penile erectile tissue is a mechanism of priapism







# Recurrent Priapism Pathophysiology

- Penile endothelial NO deficiency
- → cGMP-dependent protein kinase down regulation
- → PDE5 dysregulation
- Poor corp. smooth muscle tone control
- Prolonged erection with stimuli

Sauzeau et al; J Biol Chem 2003: 278: 9472-80 Champion et al; Proc Natl Acad Sci 2005; 102: 1661-6

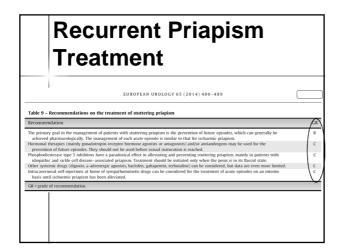
#### Recurrent Priapism Treatment

- Prevent future episodes
- Acute Rx: aspiration & α-agonists
- Hormonal manipulation
  - GnRH agonists, antagonists
  - Antiandrogens, estrogens
  - 5ARIs
  - Ketoconazole
- Duration of treatment ???
- Caution in the younger population

#### Recurrent Priapism Treatment

- Oral α-agonists
- Digoxin
- Terbutaline
- Gabapentin
- Baclofen

Gupta et al; J Urol; 1998; 159: 1529-36 Sadeghi-Nejad et al; J Urol 1997; 157:202 Priyadarshi S. IJIR; 2004; 16: 424-6



# PDE5-I & Recurrent Priapism

N= Thirteen patients SCD

- Priapism recurrences min 2x/week
- Sildenafil 50 mg or placebo daily, unassociated with sleep or sexual activity, for 8 weeks
- Followed by open-label use of this regimen for an additional 8 weeks.

# Randomized Controlled Trial of Sildenafil for Preventing Recurrent Ischemic Priapism in Sickle Cell Disease

Arthur L. Burnett, MD, MBA , Uzoma A. Anele, MD, Irene N. Trueheart, RN, John J. Strouse, MD, PhD, James F. Casella, MD

Received: March 5, 2014; Received in revise form: March 13, 2014; Accepted: March 13, 2014; Published Online: March 25, 2014

## PDE5-I & Recurrent Priapism

- >Major priapism episodes were decreased 4-fold in patients monitored "on-treatment."
- > Sildenafil systematic dosing as strategy to prevent recurrent ischemic priapism in SCD

Burnett et al, Am J Med; March 2014 epub

Prevention of Recurrent Ischemic Priapism with Ketoconazole Evolution of a Treatment Protocol and Patient Outcomes

Michael P. Hoeh, MD and Laurence A. Levine, MD

- Retrospective chart review and phone survey of 17 patients with RIP
- Primary outcome: RIP prevention KTZ
- Daily prolonged erections pre-Rx
- ER visit per pt prior to Rx = 6.5

DOSE: 200 TID + Prednisone 5.0 mg 2 wks, → KTZ 200 qhs 6 months

Prevention of Recurrent Ischemic Priapism with Ketoconazole: Evolution of a Treatment Protocol and Patient Outcomes

Michael P. Hoeh, MD and Laurence A. Levine, MD

#### ■ RESULTS:

- No pt had ER visits for priapism on KTZ
- 16 / 17 (94%) complete resolution
- Effective immediately after starting Rx
- No reported sexual AEs due to KTZ
- 1 pt stopped due to nausea / vomiting
- 14 / 16 discontinued after median 7 mo
- 29 % no recurrence;
- 78.6% partial or total resolution

Hoeh M and Levine L: J Sex Med, 2014; 11: 197-204

Prevention of Recurrent Ischemic Priapism with Ketoconazole: Evolution of a Treatment Protocol and Patient Outcomes

Michael P. Hoeh, MD and Laurence A. Levine, MD

Department of Urology, Rush University Medical Center, Chicago, IL, US

#### RIP Ketoconazole Summary:

- Reasonable efficacy / safety
- Cost advantageous
- Sexual function preserved
- Current tapered dose for 6 mo
- ? Long-term effects
- 20-25% need to stay on the medication

Hoeh M and Levine L: J Sex Med, 2014; 11: 197-204

#### **Priapism Economics**

Emergency department average cost for one priapism visit:

➤If discharged home: \$ 1778.00

➤ If admitted for hospital stay: \$41,909.00

Flum AS. J Sex Med. 2012, 9: 183-298 abs

#### **latrogenic Priapism**

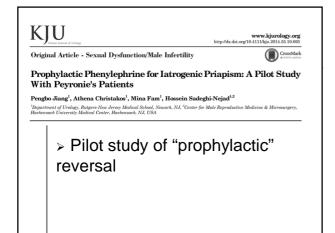
- Intracavernosal injections
  - Clinics, ED evaluation, PD evaluation
  - Many with prolonged, painful erections that require further pharmacologic injections, penile aspiration, and/or surgical intervention
  - Persistence of erection can be alarming and exceedingly uncomfortable for patients
  - Reversal more challenging hours after injection

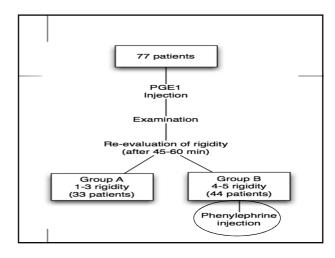
#### **latrogenic Priapism**

- "Fear" of phenylephrine
- Unfamiliarity; AE concerns
- The majority of Peyronie's patients undergoing PDDU have no or mild ED
- Ideal study group to evaluate the effects of low-dose phenylephrine as prophylaxis for iatrogenic priapism

#### **Iatrogenic Priapism**

- Retrospective review of a group of Peyronie's disease patients in our practice
- Analyze the safety and efficacy of low dose phenylephrine as prophylaxis against iatrogenic priapism



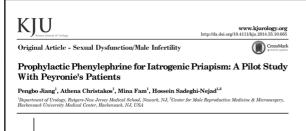


#### **Results**

- No cases of ER visit post procedure or need for aspiration
- Patients who potentially benefit from "prophylactic" phenylephrine injection can be identified based on postprocedural rigidity

#### Results

- > Group B (4-5 rigidity 15 min postprocedure) → phenylephrine (200 mcg)
- All 44 patients receiving low dose phenylephrine injection achieved complete detumescence.
- No hypotension (mean blood pressure change < 10mmHg),</li>
- > No reports of palpitations, or other AEs



>Consider "prophylactic" reversal if erection unsubsided ~ 15 min after completion of duplex Doppler ultrasound study

#### Conclusion

- Early recognition is key
- Differentiation of Ischemic and Nonischemic priapism by clinical and laboratory exam is essential
- Ischemic priapism is an emergency
- Non-ischemic : Initial surveillance

# **Conclusion- Recurrent Ischemic Priapism**

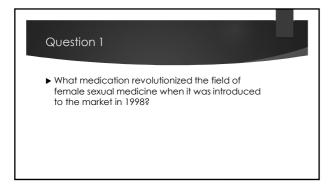
- RIP uncommon higher prevalence in special populations
- 2. PDE5 dysregulation
- Primary management goal is prevention of future episodes
- Initial Rx similar to ischemic priapism
- 5. PDE5-Is and KTZ as targeted Rx

#### **THANK YOU!**



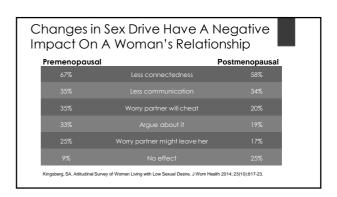


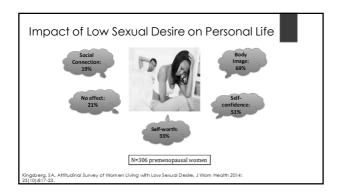


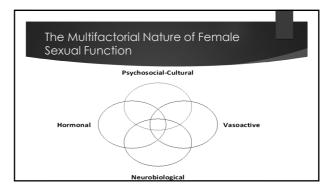


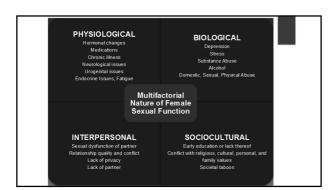


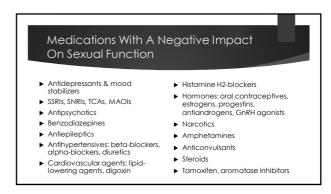


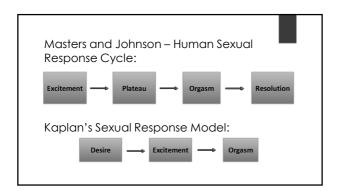




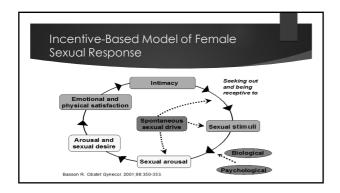




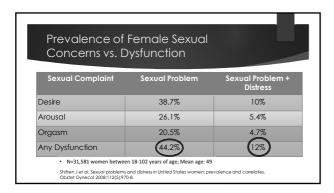


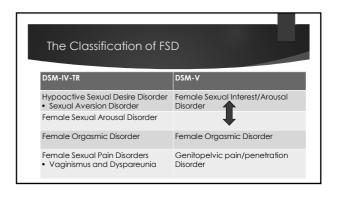


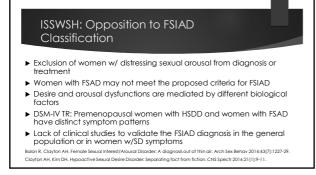


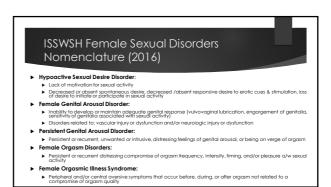


# Endorsement of Models of Female Sexual Response • Aim: to assess extent to which women endorse various models of female sexual function (Masters and Johnson, Kaplan, Basson) • N=133 pre- and postmenopausal women b/w the ages of 25-69 • Results: approx. equal proportions endorsed all 3 models. Women endorsing Basson model had lower FSFI scores • Heterogeneity of female sexual response Sand M.Fisher WA. Women's endorsement of models of female sexual response: the nurse: sexuality study. Jees Med 2007 (4)(37):08-17









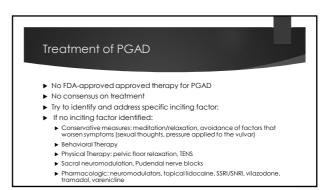
### PGAD Risk Factors

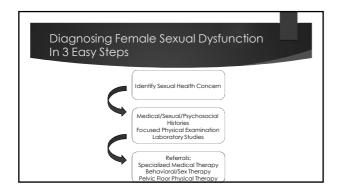
- ▶ Spinal conditions: Tarlov cysts, mass/tumor, herniated disc
- Brain pathology: Trazodone use, abrupt d/c of antidepressant, CVA, seizure disorder
- ▶ Peripheral or central trigger from increased genital engorgement
- ▶ Psychologic conditions: stress, panic disorder, anxiety disorder
- Genital pathology: vestibulodynia, VVA, clitorodynia, vulvar dermatoses, AV malformations, pudendal neuralgia, high pelvic floor tone, pelvic congestion syndrome, abnormal response to candidal infxn

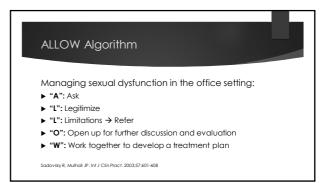
#### The Impact Of PGAD

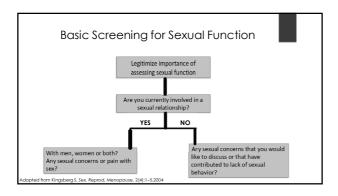
- Persistent or recurrent, unwanted or intrusive, distressing feelings of genital arousal, or being on verge of orgasm
- Symptoms a/w despair, frustration, emotional lability, catastrophizing, suicidal thoughts
- ▶ Co-occurrence of OAB and restless leg syndrome
- Change in orgasm can occur: spontaneous, recurrent, aversive, absent, delayed, muted, or not a/w pleasure, satisfaction
- ► Limited to no resolution of symptoms, or worsening of symptoms, with orgasm

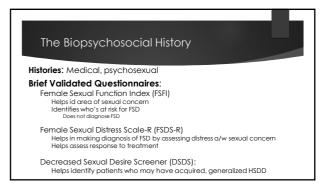
# PGAD Work Up ► History: ► Neurological or vascular disorders ► Spinal/back trauma/pelvic frauma ► Psychiatric disorders: e.g., anxiety, depression, OCD ► Medications ► Exam: ► Genital exam: trigger point testing, assess for varices ► Labs: ► Lobs: ► Low utility for making diagnosis but can check hormone levels ► Imaging: ► Pelvic uls w/doppler (varices) ► Spinal MRI, pelvic MRI, EEG

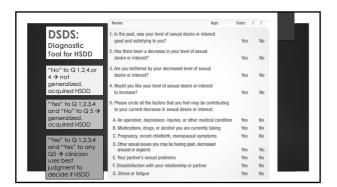


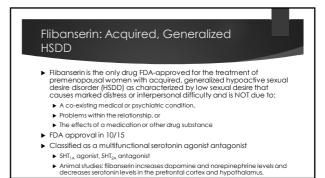


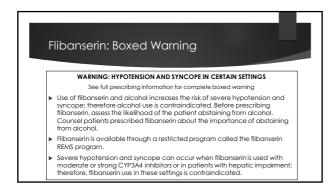


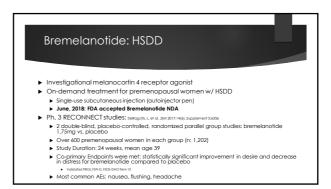












#### Genitourinary Syndrome of Menopause

- ▶ GSM is chronic and progressive
- ▶ Affects up to 50% of midlife and older women (Management of symptomatic vulvovaginal atrophy:2013 position statement of NAMS. Menopause 2013;20:888-902)
- ▶ Symptoms:
  - ► Genital dryness, burning, irritation, decreased genital arousal/orgasmic intensity
  - Poor vaginal lubrication during sex, discomfort with sex, impaired sexual function, postcoital bleeding
  - ▶ Urinary urgency, dysuria, recurrent UTIs

# Vaginal Atrophy Effects of Reinitiating Topical Estrogen Therapy

#### Tx of GSM: Vaginal Estrogen

- ▶ More effective than systemic estrogen for treating GSM
- ▶ Very low doses can be used to achieve beneficial effects on vaginal epithelium
- ▶ Low systemic absorption → minimizes impact on endometrium, breast
  - ▶ Avoid breast tenderness, endometrial stimulation, and withdrawal bleeding
- ▶ Does not relieve vasomotor symptoms or preserve bone mineral density

#### Nonestrogen Therapies: Postmenopausal VVA + Dyspareunia

#### Ospemifene (Selective Estrogen Receptor Modulator)

- ► SERM, Route: oral; Hot flushes: most frequent TEAE (6.6% vs. placebo 3.6%)
- ▶ No need for endometrial protection
- Ph 3 MCT: Ospemifine showed statistically significant improvement over placebo in lowering vaginal pH, decreasing parabasal cells, & reducing dyspareunia

  Prasterone (intravaginal DHEA):

- ▶ Approved by FDA in 11/16
- Only FDA-approved, local non-estrogen product for dyspareunia due to menopausal VVA
- Intracellular conversion of DHEA to estrogen (estradiol) and androgen
- Daily use; Minimal systemic exposure
   Has not been studied in women with breast cancer

#### Prasterone Research

- ▶ Phase III clinical trial: to confirm local effects of prasterone on moderate to severe dyspareunia (Archer DF et al.
  - Daily intravaginal prasterone for 12 weeks (6.5mg)
  - Clinically and statistically significant beneficial effects on 4 co-primary objectives of VVA (% of vaginal parabasal cells, % of vaginal superficial cells, vaginal ph., moderate to severe dyspraeunia)

    Serum steroid levels remained w/in normal postmenorange

  - Most common AE: vaginal discharge from melting suppository (6%)
  - No change in endometrial atrophy after 12 months (D. Portman, et al. Menopause 2015)

#### Low Dose Vaginal Estrogen Therapy in Women With A History Of Estrogen-Receptor Positive Breast Cancer

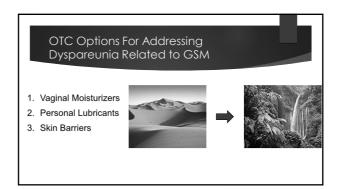
- ▶ Low-dose vaginal estrogen should be used only as 2<sup>nd</sup> line therapy if nonhormonal tx not effective
- ▶ Potential risk of small increase in circulating estrogens
- ▶ However, no increased risk of breast cancer recurrence in Al and tamoxifen users with low-dose vaginal ET during mean 3.5 yr follow up
- ▶ Decision about low-dose vaginal ET should involve oncologist

LeRay I et al. Local estragen therapy and risk of breast ca control study. Breast Cancer Res Treat 2012;135

### Use of Vaginal Estrogen In Women With A History Of Estrogen-Dependent Breast

#### ► ACOG Committee Opinion, 3/16:

- To treat the hypoestrogenic-related adverse effects of cancer therapies or of natural menopause in survivors
- Vaginal estrogen should be reserved for patients who are unresponsive to non-hormonal remedies
- Decision should be made in coordination w/a woman's oncologist
- Data does not show increased risk of cancer recurrence among women currently undergoing treatment for breast cancer or those with a personal history of breast cancer who use vaginal estroaen



#### Nonhormonal Vaginal Moisturizers

- ▶ Non-prescription, long-term relief of vaginal dryness
- ▶ Replenish water content to vagina, improves elasticity
- ▶ Longer duration of effect than personal lubricants
- Often used for the treatment of atrophic vaginitis (vaginal dryness, itching)
- ▶ Widely-available

#### Personal Lubricants

- ► Relief of vaginal dryness/dyspareunia during sexual
- ► Diminishes discomfort due to friction
- ▶ Applied around external genitalia & inside vagina
- $\blacktriangleright$  Short duration of action
- ► Types:
- ➤ Water-based
- ▶ Silicone-based
- ▶ Oil-based

#### Water-Based Lubricants

- ▶ Most widely available
- ► Safe to use with latex condoms, sex toys
- ► Tend to dry up quickly
- ▶ Reactivate with water
- ▶ Do not stain
- ▶ Rarely cause irritation
- ► Common ingredients: deionized water, glycerin, propylene glycol
- Available in glycerin-free options
- Glycerin may promote vaginal inflammation and yeast infection

#### Oil-Based Lubricants

- ▶ Petroleum-based:
- Petroleum jelly, mineral oil, baby oil
- May promote vaginal inflammation/irritation
- ➤ Not for use with latex condoms
- Can reduce both the effectiveness of latex items and prevention of STDs
- ► Natural oils:
- Coconut, avocado, comolive, peanut,
- ► Non-irritating
- Should not be used with latex items





#### Silicone-Based Lubricants

- Longer lasting than waterbased lubricants
- ► Can be used in water
- ► Safe to use with latex condoms, diaphragms, non-silicone toys
- Available in glycerin-free options
- ► Can be used as a massage
- More expensive than waterbased lubricants
- ► Harder to wash off sheets and clothing

# Vaginal Stenosis - Treatment ► Mainstay of therapy: ► Vaginal dilator ► May consider topical anesthetic, if necessary ► Vaginal estrogen ► Non-hamonal therapy is estrogen contraindicated ► Duration of therapy is variable ► "If you don't use it, you lose it" ► Pelvic Floor PT

#### Vaginal Rejuvenation

- ▶ Marketing, not medical, nomenclature
- ▶ Umbrella term to describe aesthetic and functional procedures to correct/restore the vagina and surrounding tissues
- ▶ Treatment Spectrum:
  - ► Noninvasive → lubricants, hormone therapy, kegel exercises, **energy-based systems**
  - ightharpoonup Invasive ightharpoonup vaginoplasty, labiaplasty, etc.

#### Benefits of Energy Based Systems

- ▶ Non-invasive
- ► Avoids surgical risk
- ▶ Less expensive than surgery
- ▶ Less downtime than surgery
- ► Can be performed by wider range of practitioners (e.g., NP, PA)

#### Fractional CO2 Laser: Treatment of GSM

- ► Fractional microablative CO2 laser: originally designed for tx of acne scars, skin resurfacing and rejuvenation
- ► Laser generates heat and vaporizes the water content of target cells
- ► Production of new collagen and elastic fibers, remodeling of connective tissues
- ▶ Improves vaginal elasticity and hydration of the vaginal walls/ relieves discomfort during penetrative intercourse

Perino A, et al. Vulvo-vaginal atrophy: a new treatment modality using thermo-ablative fractional CO2 laser. Maturitas 2015;80(3):296-301

#### Fractional C02 Lasers

- $\blacktriangleright$  510k cleared for the following indications:
  - incision, excision, ablation, vaporization & coagulation of body soft tissues in medical specialties
- It is <u>not</u> cleared for the treatment of vulvovaginal atrophy (VVA)

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# Practional C02 Laser Research Athanasiou.s. et al.: improvement in prevalence of normal vaginal flora (lactobacillus) in postmenopausal women & reduction in vaginal pH after 3 treatments Sokol E. and Karam M: Statistically significant improvement in vaginal pain, burning, itching, dryness, dyspareunia, and dysuria: no adverse events Sokol E. and Karam M: statistically significant improvement in VVA symptoms through 1 year following freatment Pierallia. et al: significant improvement in VVA symptoms in breast cancer survivars after 3 treatments; 52% were satisfied after 11 months. No adverse events No sham arm studies, 1 laser retreatment usually indicated after 1 year

FDA Warns Against Use Of Energy Based Devices For Vaginal Rejuvenation Procedures

#### July 30, 2018:

- ▶ Safety and effectiveness of energy-based devices to perform vaginal "rejuvenation" or cosmetic vaginal procedures has not been established
- ► FDA has not cleared or approved any energy-based medical device for vaginal "rejuvenation" or vaginal cosmetic procedures, or for the treatment of vaginal symptoms related to menopause, urinary incontinence, or sexual function
- Discuss the benefits and risks of all available treatment options for vaginal symptoms with your patients

# ► Find a FSD specialist in your area: www.isswsh.org ► Find a pelvic floor physical therapist in your area: www.apta.org ► Find a certified sex therapist in your area: www.aasect.org www.sstarnet.org



#### Genital surgery for the MtF Transgender patient

Robert Oates, MD

Boston Medical Center Boston University School of Medicine

#### **Disclosures**

- No industry relationships to disclose
- No financial relationships to disclose

#### Transgender Care at Boston Medical Center

- Center for Transgender Medicine and Surgery (CTMS)
  - Coordination of care
  - Multidisciplinary approach
    - Endocrinology, Urology, Plastic Surgery, Internal Medicine, Nursing
    - $\blacksquare$  Psychiatry, Behavioral Therapy, Social Work, Physical Therapy
    - Gynecology, Podiatry, ENT, Dermatology, Surgical Oncology
  - Indication/Approval Committee
    - Endocrinologist, Urologist, Plastic Surgeon, Nurse Practitioner ■ Social Worker, Psychiatrist, Team Leader (Internist), Coordinator
  - Financial
    - Surgeons and clinic / hospital

#### Types of 'Bottom Surgery"

- Orchiectomy
- Neovaginoplasty
- "Genital Remodeling" (zero-depth vaginoplasty)

#### Goals of Surgery: Orchiectomy

- Alignment of anatomy with body image

  Slightly less scrotal bulk
- Relief of psychological discomfort
- . The knowledge there are no testicles
- Elimination of spironolactone Used in conjunction with estrogens
  - Blocks testosterone action/production
  - Has intrinsic estrogenic effect
- Improved estrogenic effect
  - If leydig cells not totally suppressed
- May be prior to full surgery
  - Neovaginoplasty / Genital Remo Do not remove scrotal skin
- Will not compromise future surgery Neovaginoplasty / Genital Remode
- Need to ask about parenthood!

# Surgical Technique: Orchiectomy

#### Untoward events after orchiectomy

- Scrotal hematoma
  - rare
- Incision breakdown
  - rare
- Discomfort at end of spermatic cord
  - unusual

- Decreased libido and erection
  - Depends on level of pre-op T
  - If high, may experience hypogonadism
  - If castrate, essentially no change
- Decreased ejaculate volume
  - Depends on level of pre-op T
  - If high, may experience reduction
  - If castrate, essentially no change

#### Goals of Surgery: Neovaginoplasty

- Alignment of anatomy with body image
- Relief of psychological discomfort
- One of the final stages of genderconfirming process
  - Augmentation mammoplastyFacial feminization
- Feminine appearing vulva
- Hooded and sensate clitoris
- Urethral meatus properly located
- Vaginal depth sufficient for penetration (Neovaginoplasty)
  - If necessary

#### Goals of Surgery: vaginal depth

- Heterosexual orientation
  - Penetrative intercourse ■ Amount of tissue available

    - Penile
    - Scrotal
    - Lower abdomen Peritoneum
    - Colon
- Lesbian Orientation
  - Penetrative sexual activity
    - Toys / dildos ■ "How deep?
  - Non-penetrative sexual activity
    - Still desirous of vagina
    - "How deep?"

### Desired Outcomes: Neovaginoplasty

- Improved mental health scores after surgery (GRS or FFS)
- Good satisfaction with appearance and self image
- Lowers dysphoria
- Improved well-being
- Clitoris with dorsal hooding- sensate
- Mucosal strip: well perfused
- Proper urethral function / location
- Labial symmetry
- Functional vagina

#### Important to individualize !!

#### Patient Selection: CTMS at BMC

- Established dx of gender identity disorder (F64.0)
- Two letters of recommendation
- 18 years or older
- Hormonal therapy of >1 year
- Real-life experience for >1 year

- BMI < 32
- Non-smokers
- Non-diabetics At least well-controlled
- Good general health
- Genital hair removal

#### Patient Selection: CTMS at BMC

- Follow WPATH Guidelines
  - World Professional Association for Transgender Health
- Slight local modifications
  - Smoking, BMI considerations, when to stop estrogens, etc

#### Preoperative requirements: Neovaginoplasty

- Genital hair removal
  - Penile and scrotal skin
  - Midline distribution
  - Base of scrotum down to anus (2" strip)
  - NOT lateral to penis or scrotum
- Laser hair removal
- Electrolysis
- Some insurers may cover cost



#### Preoperative requirements : Neovaginoplasty

- Discontinue estrogen 4 weeks prior
  - To prevent DVTs
  - No hard data to support
- Bowel prep day before
  - In event of rectal injury



### Relevant anatomy: Neovaginoplasty

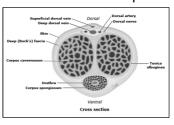


Skin Superficial fascia (dartos)

Deep fascia (Buck), urethra/corpus spongiosum Spermatic cord

Superficial transverse perineal muscle

#### Cross section of the penis



#### Vascular and neural anatomy

#### VASCULAR

#### ■ Deep

- Internal pudendal a.
  - Perineal a.Scrotal a.

  - Common penile a.Dorsal a. of penis
- Superficial External pudendal a.
  - SuperficialDeep

#### NERVE

- Deep ■ Pudendal nerve (S2-S4)

  - Perineal n.Dorsal n. of penis
- Superficial
  - Ilioinguinal n.
  - Genitofemoral n.







- □ Epidural catheter
- Lithotomy position
- Perioperative antibiotics
  - cefazolin
  - □ metronidazole



#### Surgical Technique: Neovaginoplasty

- Markings
  - □ Perineal flap
  - □ Scrotal skin



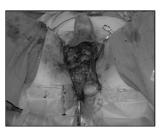
#### Surgical Technique: Neovaginoplasty

- □ Elevation of perineal flap
- $\hfill \square$  Deepithelialization of scrotal skin  $\ensuremath{\text{\fontfamily{1.5}}}$  May be used as a free graft
  - Attached to "top" penile skin



#### Surgical Technique : Neovaginoplasty

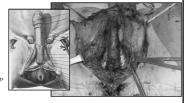
- □ Orchiectomy
  - □ Take cord at external ring
  - Specimens to pathology



#### Surgical Technique: Neovaginoplasty

- Penile dissection
  - Move tissues laterally

  - Overlying bulbospongiosis muscle
     Down into perineum
  - □ Expose both corpus cavernosa



- Bulbospongiosis muscle
  - Originates laterally
  - □ Attaches in midline raphe
  - Simply surrounds corpus spongiosum

    - Anteriorly
       Finger can be inserted in that space to elevate and allow cautery dissection off
  - Complete removal into perineum



- Dissection of neo-vaginal canal
- Take down midline perineal body below sponge
- $\hfill \square$  Dissect lateral to this as well
- Push corpus spongiosum anteriorly
- Push rectum posteriorly
- □ Gently, Gently, Gently create more space Superiorly to above trigone



#### Surgical Technique: Neovaginoplasty

- Cauterize bleeding points
  - Recto-urethralis muscles
  - External rectal serosal vessels
- May irrigate rectum
  - Betadine solution
  - □ If not sure of rectal wall integrity
- $\ensuremath{\text{\ \ \ \ \ }}$  Pack with lap pad and move to penile



#### Surgical Technique: Neovaginoplasty

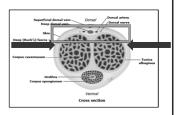
- Degloving of penis
- □ Leave dorsal hood a circumcision incision
- Creates penile skin tube □ Forms neovagina



#### Surgical Technique: Neovaginoplasty

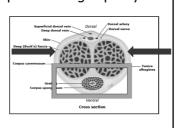
- Deconstruction of penis
- Separation of urethra
- Lateral opening on each corpora
- Removal of cavernosal tissue
- Create strip of dorsal tunica
  - NV bundle intact

  - Some prefer to dissect NV bundle to root
     Glans intact on top
     Will become neoclitoris
  - Will become ne



#### Surgical Technique: Neovaginoplasty

- Ventrally
  - Corpus spongiosum
    - Urethra and catheter







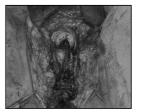
- □ Formation of neo-clitoris
  - Remove glans tissue
  - □ Create inverted V





#### Surgical Technique: Neovaginoplasty

- □ Inset of neo-clitoris
  - □ Tack to underlying tissue
  - Between adductor longus tendons



#### Surgical Technique: Neovaginoplasty

- □ Inset of urethra
- Anatomically correct position
- $\hfill \square$  Midline and straight



#### Surgical Technique: Neovaginoplasty

- □ Mature urethra
- Mature neo-clitoris
- □ Mucosal strip up to neoclitoris
- □ Inset of perineal flap
  □ Into penile skin tube



#### Surgical Technique: Neovaginoplasty

- Preparation of skin graft
- Scrotal skin removed at beginning
- Tubularized



- Inset of skin graftAttached to penile skin tube
- Whole construct invertedNeovaginal space
- □ Tailor-tacking of labia majora



- Packing : Important
- Inserted into neovagina
- Keeps it distended and in place
- □ Fixes it to surrounding tissues
- Allows free graft to vascularize



#### Surgical Technique: Neovaginoplasty

- Keeps everything in place
- Compression on mucosal strip



#### Postoperative Care

- Regular diet
- Antibiotics x 24 hrs
- Bed rest x 2 days
- Epidural removed on POD#2
- Discharge home POD#3
- Packing and foley removed on POD#6
- Dilation starts immediately after packing is removed

#### Untoward postoperative events - literature review -

#### SHORT TERM

- Infection (4-16%)
- Bleeding (2-10%)
- Necrosis (0.6-24%) UTI (4.4%)
- Urinary retention (12.8%)
- Prolapse (4.4%)
- Urethral injury (1.1-3.6%)
- Rectal injury (0.4-4.5%) Recto-neovaginal fistula (1-3%)

#### LONG TERM

- Neovaginal stenosis (1-12%)Urethral fistula (1.7%)
- Abnormal urine stream (10-20%)
- Meatal stenosis (1-40%)
- Partial prolapse (1-4%)
- Need for secondary corrections (33.7)
   Need for revision vaginoplasty (2.9%)

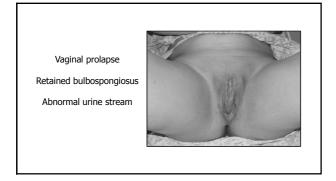
Vaginal canal necrosis

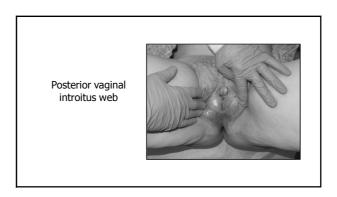


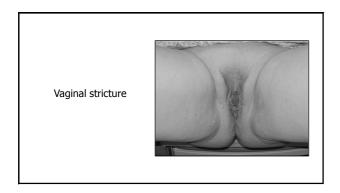
Hematoma requiring transfusion Urethral strip slough

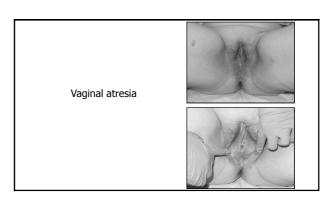


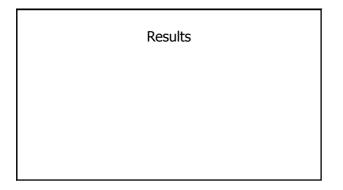


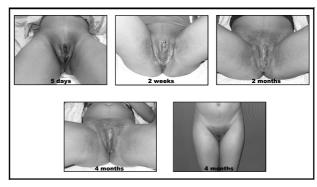


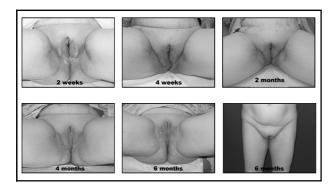












#### Goals of Surgery: Genital Remodeling

- Alignment of anatomy with body image
- Relief of psychological discomfort
- One of the final stages of gender-confirming process
  - Augmentation mammoplastyFacial feminization
- Feminine appearing vulva / labia
- Hooded and sensate clitoris
- Urethral meatus properly located
- No vagina

  - No need for dilation
    No need for hair removal
  - No complications from the vagina

#### Goals of Surgery: Genital Remodeling

- Older individuals
- No desire for penetrative sexual activity
- No "need" for the vagina
- Strong "need" for feminine appearance
- Discharge following day
- Foley and compressive dressing ■ Remove POD#5

Excellent option for some patients: not everyone requires full neovaginoplasty

#### Conclusion

- Neo-vaginoplasty is an established component of treatment of gender dysphoria
- Penile inversion neo-vaginoplasty is an established gold-standard technique
- Growing demand

#### **Future Directions**

- More outcome studies are necessary
- Need for formal education and training of surgeons
- Multidisciplinary approach to care of patients with gender dysphoria

#### thank you

#### **Cancer of the Testis**

Joel Sheinfeld, M.D.
Florence & Theodore Baumritter/
Enid Ancell Chair of Urologic Oncology
Deputy Chief Urology Service
Memorial Sloan Kettering Cancer Center

#### Disclosure Statement

Nothing to disclose

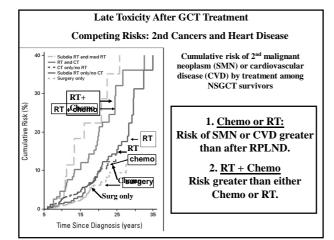
#### Testicular Cancer Trends in Survival for all Stages

Years	5-yr Survival (%)
1960 - 63	63
1970 - 73	72
1974 - 76	79
1977 - 79	88
1983 - 88	93
1989 - 96	95
2005 - 11	97

**Reducing Morbidity and Testing Lower Bounds of Efficacy** 

#### Germ Cell Tumors: Special Features (overall 5 year survival ~ 97%)

- Occurrence in young adults
  late toxicity (2<sup>nd</sup> malignancies, CV events)
  late relapse (> 2 years after CR)
- Chemosensitive
- Consistent pattern of metastasis
- Produces marker proteins (AFP/ HCG)
- · Capacity to differentiate: teratoma



#### **Testicular Tumors Epidemiology**

Approximately 8,500 new cases in US in 2018

Approximately 350 deaths in US in 2018

Most common solid malignancy in men ages 15-34 years

Incidence increasing worldwide; more than doubled in last 40 years

Germ cell tumors: 96%

2-3% incidence bilateral tumors

#### Frequency of Germ Cell Tumor Histology

<u>Histology</u>	Frequency	Stage I	Stage II	Stage III
Seminoma	50%	70%	20%	10%
Cure Rate		99%+	~98%	~90%
NSGCT	50%	33%	33%	33%
Cure Rate		99%+	~90%	70%-80%

#### **GCT: Risk Factors**

#### Cryptorchidism

3-14 times increased incidence

5% - 10% develop tumor in normally descended testicle

Atrophic testicle

Infertility/subfertility:10%-15% GCT diagnosed during fertility w/u

Family history: 8-10 fold increased risk for brothers; 4-6 fold increased risk for fathers and sons

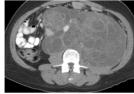
Cannabis ??

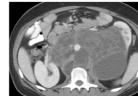
#### **Testicular Tumors: Diagnosis**

A solid, firm, intratesticular mass is testicular cancer until proven otherwise. Radical orchiectomy is indicated.

<u>Delay in diagnosis very common</u> and can result in more advanced stage, increased burden of therapy and decreased survival (NSGCT).

#### Delay in diagnosis: patient +/- physician(s)





GI symptoms for 4 months

Back pain for 8 months

#### **Testicular Tumors--Presentation**

#### <u>LOCAL</u>

Painful swelling, dull ache

Hard firm painless mass (pathognomonic)

#### **METASTATIC SITES**

Back pain (RP metastasis)

Neck mass [supraclavicular node(s)]

Cough (pulmonary metastasis)

GI symptoms (mass)

CNS symptoms (brain metastasis)

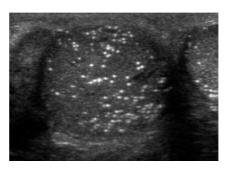
Lower extremity swelling (iliac or IVC thrombus)

Gynecomastia 5%-10% cases

# Scrotal sonography with doppler images hypoechoic vascular lesion(s)

Solid intratesticular mass is a tumor until proven otherwise. Rx is radical orchiectomy

#### microlithiasis



#### A 5-Year Followup Study of Asymptomatic Men With Testicular Microlithiasis

Brian J. DeCastro, Andrew C. Peterson\* and Raymond A. Costabile
From the Department of Urology, Madigan Army Medical Center, Tacoma, Washington, and Un

Purpose: Testicular microlithiasis is an imaging entity of the testicle with questionable significance as a marker for testicular cancer [4, 200] we reported on a large prespective screening study establishing the prevalence of testicular microlithiasis tooks 5.6% a healthy asymptomatic population of Army volunteers 18 to 35 years old. In contrast, testicular cancer develops in these of 100 years of the service of the serv

	Comparison of followup studies			
	No. Pts With TM (%)	No. Pts Contacted/ Total No. Pts (%)	No. Pts With TC (%)	No. Pts/Total No. Performing Self-Examination
Original study (2000) 2-Yr followup (2002) 5-Yr followup (2005)	84 (5.6) 84 80	Not available 64/84 (76.2) 63/80 (78.8)	0 (0) 0 (0) 1/63 (1.59)	Not available Not available 29/45 (65)

<u>Conclusion</u>: Testicular cancer will <u>NOT</u> develop in majority of men with microlithiasis with follow-up of 5 years. Intensive screening not cost effective. Recommend self-examination in men at risk.

Testicular Microlithiasis Predicts Concurrent Testicular Germ Cell Tumors and Intratubular Germ Cell Neoplasia of Unclassified Type in Adults

A Meta-Analysis and Systematic Review

 $Iain \ B. \ Tan, MD^1; \ Kai \ K. \ Ang^1; \ Boon \ C. \ Ching, \ MD^2; \ Chandra \ Mohan, \ MD^3; \ Chee \ K. \ Toh, \ MD^1; \ and \ Min \ H. \ Tan, \ MD^1$ 

BACKGROUND: There is an increasing body of literature associating testicular microlithiasis (TM), a common finding on testicular ultrasound, with testicular germ cell tumor (TGCT) and intratubular germ cell neoplasis of unclassified type (TGCNU). Determining these associations is pertinent both clinically and biologically. To the author's knowledge, no previous systematic review or meta-analysis has been performed. METHODS: A comprehensive systematic literature review was performed without language restrictions through July 2009 and included an exhaustive search of electronic databases and article references. Two reviewers extracted data independently. Studies were categorized according to the clinical context in which sonography was performed. The primary study outcomes were concurrent diagnoses of TGCT or TGCNU, with TM. In addition, studies with prospective follow-up of patients with TM were reviewed. RESULTS: Thirty-three studies met inclusion criteria. TM were 100 sosciated with an increased risk of TGCT in asymptomatic men. However, in referral populations, TM was associated overall with a risk ratio of 85. (95% confidence interval (CI), 45-161, P < .001) for a concurrent diagnosis of TGCT and 10.5 (95% CI, 53-20.8; P. < .000) for 15CNU. Seventeen observational studies were identified in which the interval devoloment of TGCT in patients with

Sperm banking and testicular surgery

Sperm banking PRE - orchiectomy

Solitary testicle

Bilateral masses

History of contralateral orchiopexy

Atrophic contralateral testicle

#### **Testicular Tumors: Clinical Evaluation**

**History / Physical Exam** 

**Scrotal US** 

Serum AFP, HCG, LDH

CT Abdomen, Pelvis

CT Chest vs CXR

MRI brain: pure choriocarcinoma; neurologic sxs



•no role in initial staging

no better accuracy over CT

•post-chemo seminoma

(does not distinguish teratoma from fibrosis)

#### PET SCAN in LOW-STAGE GCT

NO ROLE in staging or follow-up of low stage GCT

Excess radiation; excess \$\$\$

Adherence to National Comprehensive Cancer Network

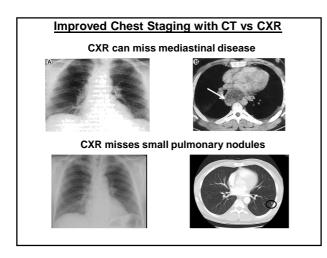
**Guidelines for Testicular Cancer** 

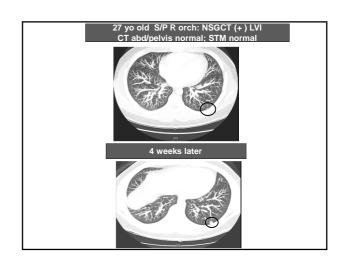
in M. Wymer, MD¹, Shane M. Pearce, MD², Kelly T. Harris, MD³, Phillip M. Pierorazio, MD³, Siamak ieshmand, MD⁴, Scott E. Eggener, MD². ♣ ·

27% of patients with inappropriate PET scan had Stage I GCT (NSGCT >> Seminoma)

5% of CSI patients had inappropriate PET scan

Wymer et al. J Urol; 2016





#### Testicular Cancer Serum Tumor Markers

•Diagnosis

•Staging (TNMS)

- Monitoring <u>response</u> to therapy
- •Monitoring for tumor recurrence
- •Predicting prognosis and risk-directed therapy

(in both low stage and advanced GCT)

#### **Serum Tumor Markers**

**HCG** 

**AFP** 

Produced by syncytiotrophoblasts

Embryonal cell; yolk sac

Excludes diagnosis seminoma

Half-life: 18-36 hours

Half-life: 5-7 days

False positive

Cross-reaction LH

Treatment induced hypogonadism Pituitary production of HCG

**Testosterone suppression test** 

Seminoma ~ 10% elevated (no prognostic impact)



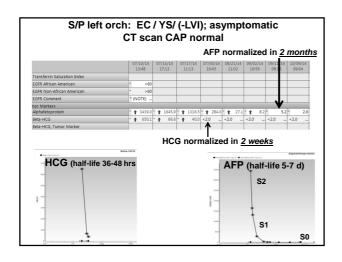




left orch: EC / YS / (-)LVI 3 days post – orch: HCG: 66.6; AFP 1655 CT CAP: NORMAL S/P left orch: EC / YS/ (- LVI ); asymptomatic CT scan CAP normal

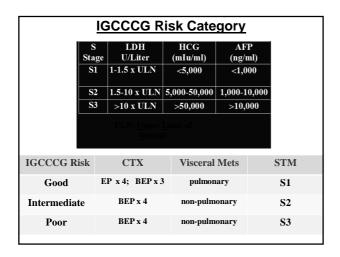
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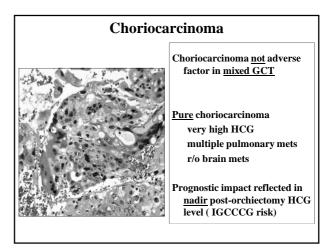
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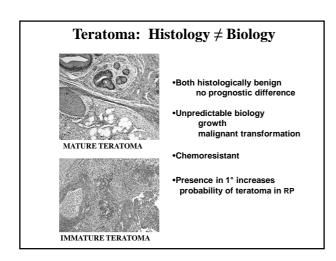


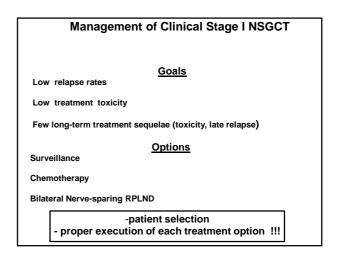
Serum Tumor Markers				
IGCCCG Risk Group	<u>Good</u> <u>S1</u>	<u>Intermediate</u> <u>S2</u>	<u>Poor</u> <u>S3</u>	
AFP	< 1000	1000-10,000	> 10,000	
HCG	< 5000	5000-50,000	> 50,000	
LDH	< 1.5x	1.5-10x	> 10x	
Chemotherapy	BEPx3 EPx4	BEPx4	BEPx4	
Chemotherapy regi	imen based	on IGCCCG risk	group	

Marker status (S1-3) based on post-orchiectomy nadir









### Clinical Stage I NSGCT what is risk of relapse??

	<b>Factors</b>	<b>Treatment</b>	Relapse	<u>NED (%)</u>
ŀ	→No LVI (I-A)	observe	~15%	~99%
	LVI, T1-4 ( <u>I-B)</u>	observe	~45%	~99%
l	→↑STM, T1-4 <u>(I-S)</u>	observe or RPLND	~99%	~99%

#### Clinical Stage IS Elevated Serum Tumor Markers (STM)

Usually reflects systemic disease and patients should receive 1° chemotherapy

<u>↑STM pre-RPLND</u> is predictive for:

- 1. Systemic relapse (100%) in clinical stage I S (*J Urol 152:111, 1994*)
- 2. Relapse in low volume (pN1) RP disease (J Clin Oncol 19:2020, 2001)
- 3. Persistent NSGCT (↑ STM) in high volume (pN2/3) RP disease

(Proc ASCO 18:308A, 1999)

# Clinical Stage I – II NSGCT Elevated Serum Tumor Markers (pre-RPLND) Usually reflects occult systemic disease

<u>Author, ref</u>	Relapse Rate (%)
Socinski et al: J Urol, 1988	60%
Rabanni et al: JCO, 2001	80%
Stephenson et al: JCO, 2005	72%
AVOID 10 PR	I ND

AVOID 1º RPLND
THESE PATIENTS SHOULD RECEIVE INDUCTION CTX

#### Clinical Stage I NSGCT

#### Surveillance

Number of evaluable pts 2, 587

Patients with NED 2,169 (>98%)

Number of relapses (all pts) 759 (29%)

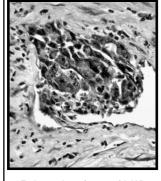
CS IA (Absence of LVI) <15%

Median time to relapse 7 (4-13) months

Vergouwe Y et al; JCO 21: 4092; 2003

• Curability of relapsed chemo-naive patients •Increased burden of therapy ? • Compliance !!!

**Embryonal Carcinoma and LVI** 



predicts for relapse on surveillance or pN+ at RPLND

NO ADVERSE PROGNOSTIC IMPACT IN ADVANCED NSGCT !!!

Embryonal carcinoma with LVI

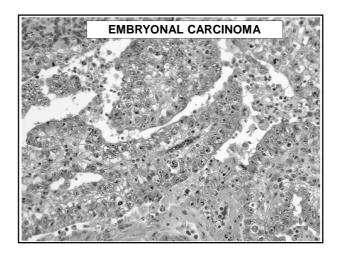
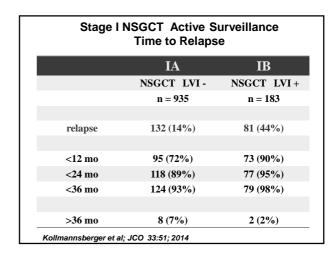
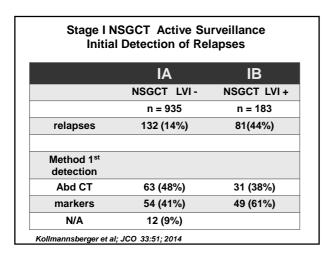
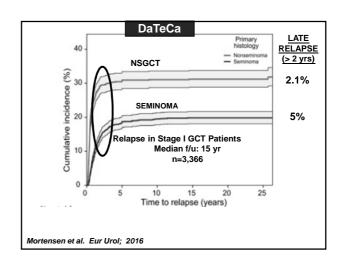
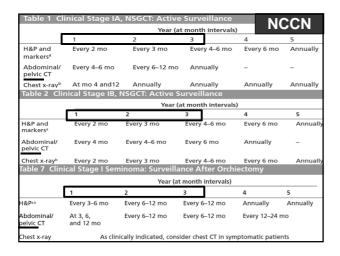


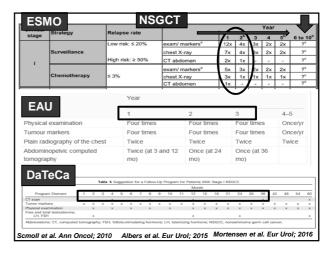
Table 2. Pooled Univariab	le Odds Ratios for Predictors of Occult	metastas			Occult Metasta
		No. of	Patients With	resence or	DC Cult Ivietast
Predictor	Study References No.	Patients	Characteristic (%)	OR	95% CI
/ascular invasion	,				
Venous, presence v absence	17.19.22.33.43.47	1.007	42	4.7	25 to 8.5
Lymphatic, presence v absence	17 19 22 43 47	853	18	5.4	3.0 to 1
Venous or lymphatic, presence v absence	6 19 20 23 25 26 29 32 35 39 48 50-53	1.364	36	5.2	4.0 to 6
listology of primary tumor					
Embryonal carcinoma				$\overline{}$	
Presence v absence	6,17,19,26,33,43,48,50,51	1505	85	( 2.9 )	2.0 to 4.
> 50% v ≤ 50%	20,39,49,50,52			$\smile$	1.7 to 4.
Yolk sac					
Presence v absence	6,17,19,26,32,33,35,43,52,53	1,599	52	0.91	0.68 to 1
Mature teratoma					
Presence v absence	19,26,52,53	434	45	0.48	0 27 to 0.
Differentiated teratoma					
Presence v absence	17, 43	595	6	0.13	0.02 to 0.
Pathologic stage of primary tumor					
pT2-4 v pT1	17,29,32,33,43,50	1,066	22	2.6*	1.8 to 3.
Size of primary tumor,† cm					
>3 v ≤3	16,19,20,22,26	594	68	1.5	0.99 to 2
AFP serum level					
⊟evated v normal	16,20,24,26,29,33,52,53	990	40	0.94	0.59 to 1
HCG serum level					
⊟evated v normal	16,20,22,33,52,53	550	32	1.1	0 49 to 1
Patient age ‡ years					
>30 v <30	16,20,22,43,53	683	41	1.6	1.2 to 2.
MB-1 staining, % of cells					
> 70 v ≤ 70	35,39,49	212	55	4.7	2.0 to 1
Abbreviations: NSGCT, nons eminomatous testicular p	perm cell tumor; OR, odds ratio; AFP, alpha-fetoprot	ein; H C G, hur	nan chorionic gonadotro p	hin; MIB-1, mo	nocional antibo
the human nuclear cell proliferation-associated antiger					
*Heterogeneity of effect: surveillance studies:		tudies: odd	s ratio, 40 (95% CI, 2.	5 to 7.7).	
†Tumor size > 3 cm in references 16.19.20.22; > 3					
‡Age > 29 years in references 16,20,22; >30 years	irs in references <sup>43,53</sup> .				











CT Chest: no role; CT pelvis: very low yield (selected cases)

Abdominal Imaging: CT vs MRI??

Both require significant expertise

Far more experience with CT scans (↑↑ radiation exposure)

MRI: ↓↓↓ radiation exposure; ↑↑↑ \$\$

SWENOTECA has used for > 5 years

TRISST trial: 4 arm-double randomized noninferiority trial

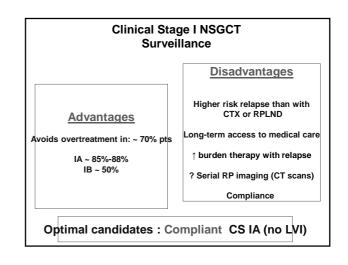
3 CT vs 3 MRI (6, 18, 36 mo)

7 CT vs 7 MRI (6, 12, 18, 24, 36, 48, 60 mo)

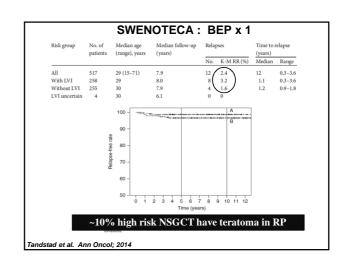
MRI probably not ready for routine use in most centers now

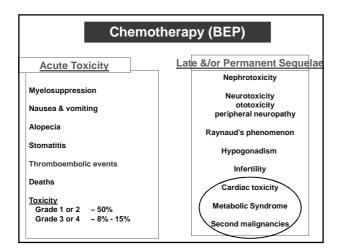
Stage I NSGCT: Active Surveillance IGCCCG Risk of Relapses			
	NSGCT LVI+	NSGCT LVI-	
	n = 183	n = 935	
relapses	81 (44%)	132 (14%)	
IGCCCG risk			
Good	76 (94%)	116 (88%)	
Int	3 (4%)	13 (10%)	
Poor	2 (2%)	3 (2%)	
STATUS			
NED	79 (98%)	126 (95%)	
DOD	-	3 (2%)	
Rx death		2 (2%)	

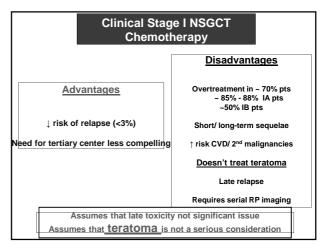
Stage I GCT Active Surveillance IGCCCG Risk of Relapses			
	NSGCT LVI +	NSGCT LVI -	SEMINOMA
	n = 183	n = 935	n = 1,344
relapses	81 (44%)	132 (14%)	173 (13%)
IGCCCG risk			
Good	76 (94%)	116 (88%)	171 (99%)
Int	3 (4%)	13 (10%)	2 (1%)
Poor	2 (2%)	3 (2%)	
STATUS			
NED	79 (98%)	126 (95%)	171 (99%)
DOD		3 (2%)	
Rx death		2 (2%)	1 (<1%)
Kollmannsberger et al; JCO 33:51; 2014			

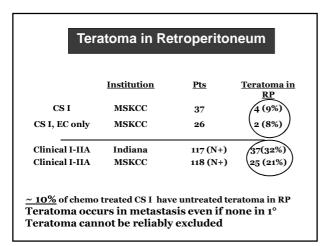


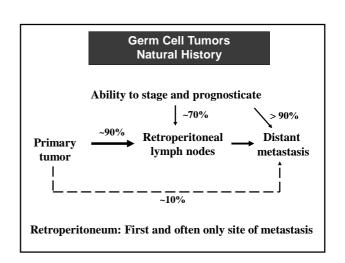
	Clinical Stage I NSGCT Risk Adapted Chemotherapy				
Author	Risk factor	Regimen	<u>No.</u>	Relapse	Median f/u (mo)
Pont	VI	BEPX 2	74	2 (2%)	79
Cullen	LVI, EC YS	BEP X 2	114	2 (2%)	48
Böhlen	LVI, EC, pT2+	BEP X 2 PVB X 2	58	1 (2%)	93
Maroto- Rey	LVI, EC	BEP X 2	231	3 (1%)	36
Klepp	LVI	BEP X 2	32	1 (3%)	40











#### **RPLND**

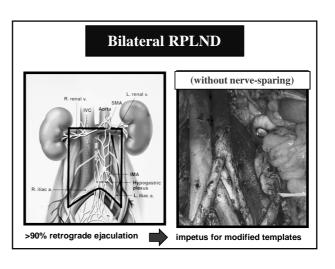
RPLND remains a critical component in the management of selected patients with GCT

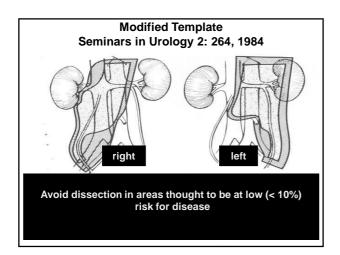
Properly performed, RPLND is both a staging and therapeutic procedure, but it should <u>ALWAYS</u> be done with <u>THERAPEUTIC INTENT</u>

Despite effective cisplatin-based chemotherapy, the potential consequences of untreated RP metastasis:

late relapse re-operative surgery somatic transformation of teratoma

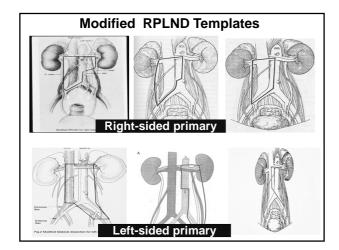
**INFERIOR SURVIVAL** 

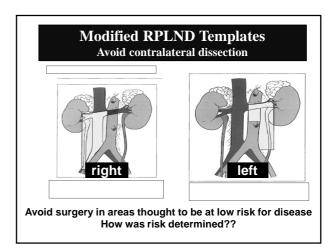


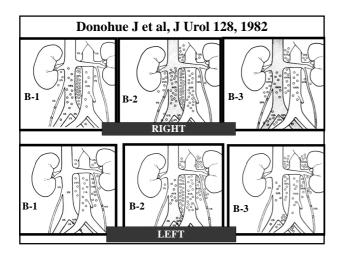


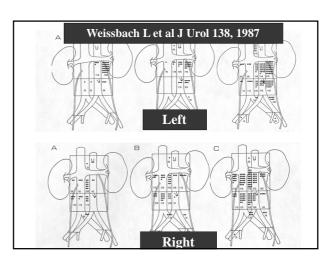
#### **Modified RPLND Templates**

- Lange PH et al; Sem Urol, 1984
- Fossa SD et al; Eur Urol 1984
- Pizzocaro G et al; J Urol 1985
- Weissbach L et al; J Urol 1987
- Sherlog A et al; Urology 1989
- Richie J et al; J Urol 1990
- Donohue J et al; J Urol 1993
- Holtl L et al; Urology 2002









Mapping Studies: <u>Underestimate</u> Retroperitoneal Disease <u>cannot assess incidence of unresected RP disease</u>

1. Without adequate clinical follow-up

 author, yr
 no.
 follow-up

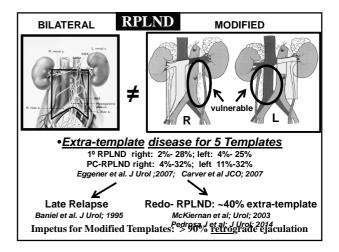
 Whitmore, 1973
 283
 none

 Donohue, 1982
 104
 none

 Weissbach, 1987
 214
 22 mo. pN0 (I)

 42-44 mo. pN+ (II)

2. In patients who received postoperative chemotherapy Weissbach study: PSII patients: PVB x 2 vs PVB x 4



#### **Late Relapse of Testicular Cancer Clinical Presentation** SITES OF LR # of sites Baniel George Sheinfeld (n=143)(n=81)(n=83)39 (47%) RP 43 (53%) 118(83%) 71 (58%) 10 (12%) 8 (10%) 14 12%) 16(11%) 8 (10%) 7 (8%) 13(10%) 10 (8%) neck

Baniel et al JCO 1995; Geldart et al BJUI 2006; Dieckmann et al J Urol 2005;

Ravi et al BJUI 2003; George et al JCO 2003; Sheinfeld AAGUS 2018

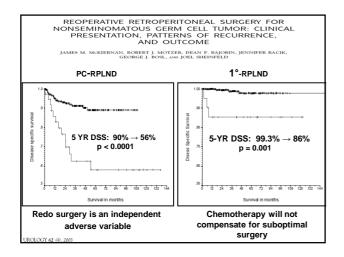
Somatic Transformation of Teratoma

Definition: Components of teratoma that histologically resemble a somatic malignancy. (e.g., PNET, enteric adenocarcinoma, rhabdomyosarcoma)

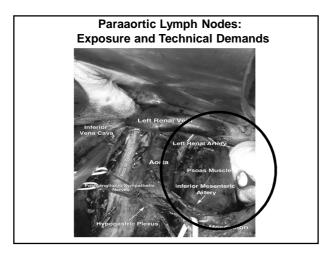
1° RPLND 0.4%
PC - RPLND 3%
Redo RPLND 18%
Late Relapse 21%

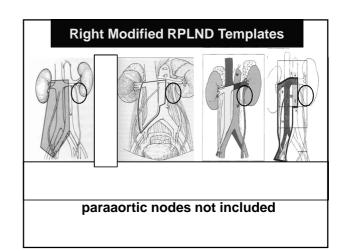
LR: 8-10X increased incidence compared to PC-RPLND ~12% in surveillance failures (no prior CTX)

REDO RPLND: 6-8X increased incidence



REOPERATIVE RETROPERITONEAL SURGERY FOR NONSEMINOMATOUS GERM CELL TUMOR: CLINICAL PRESENTATION, PATTERNS OF RECURRENCE, AND OUTCOME JAMES M. McKIERNAN, ROBERT J. MOTZER, DEAN F. BAJORIN, JENNIFER BACIK, GEORGE J. BOSL, AND JOEL SHEINFELD • Late relapse > 50% Pathology teratoma: at initial RPLND - 54%; at redo-RPLND - 56% somatic transformation of teratoma at redo: 20% Redo after 1° RPLND PC-RPLND · Increased burden of therapy additional chemotherapy 86% 50% adjunctive procedures 63% 71% Extra-template relapse ~ 40% (para-aortic most common)





#### 1° RPLND

**Extra-Template Disease for 5\* Templates** 

Eggener SE et al, J Urol 177, 937; 2007

RIGHT LEFT 2% - 28% 4% - 25%

increases with clinical and pathological stage

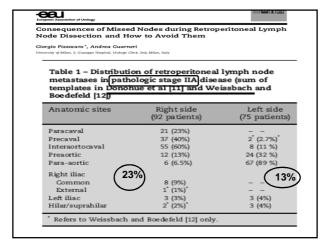
Histologic distribution of extra-template disease virtually identical to in-template disease

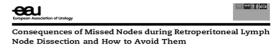
Weissbach L J Urol 138, 1987 Nelson JB Urology 54, 1999

#### Negative Ipsilateral Nodes Contralateral Disease Only

Laterality	Right	Left
T.	20/	<b>70</b> /
Eggener	3%	5%
Weissbach	3%	5%
Leibovitch	6%	3%

Eggener S et al, J Urol, 2007 Weissbach L et al, J Urol 138, 1987 Leibovich BC et al, J Urol 167: 683A, 2002

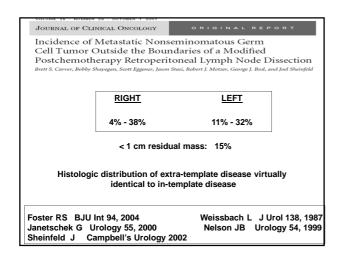


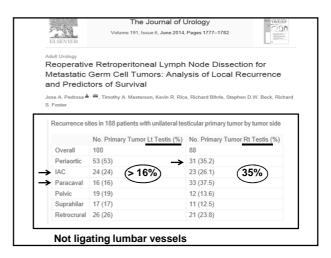


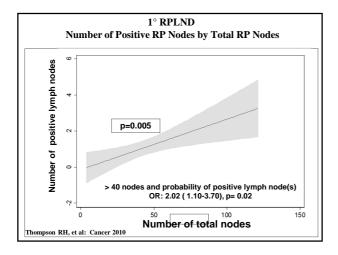
Giorgio Pizzocaro\*, Andrea Guarneri

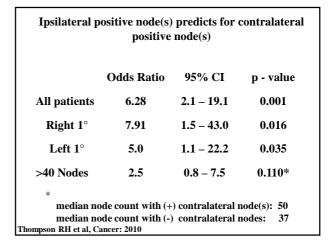
#### 4. Conclusions

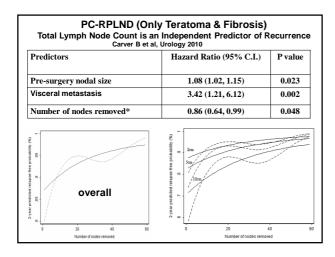
The only conclusion is that landing zones for retroperitoneal lymph node metastases are too scattered to design a restricted template that will allow radical RPLND and an easy nerve-sparing technique to maintain antegrade ejaculation. If a restricted template is used, missed nodes are to be expected, and extratemplate metastases are not the fault of the template but a responsibility of the surgeon. We have also to bear clearly in mind that chemotherapy is not a panacea for missed or recurrent nodal metastases (memento teratoma) and that prospective nerve-sparing surgery is not only technically demanding but is also safer than templates.

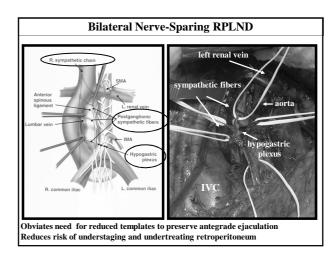


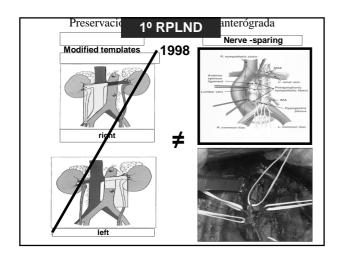


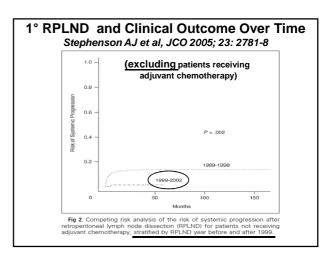


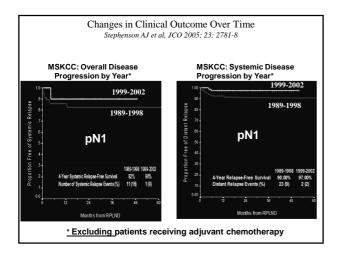


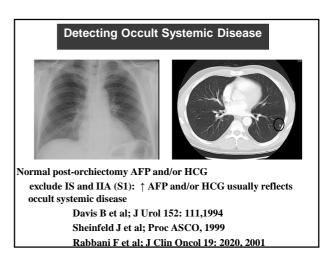




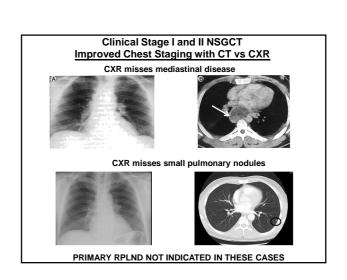


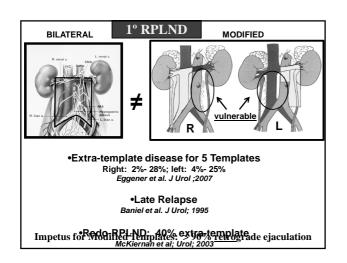






# Extra - template and/or Contralateral GCT in the RP RP mapping studies always underestimate RP disease Ipsilateral disease predicts for contralateral GCT Thompson et al, Cancer 2010; Donohue et al, J Urol 1982 Variable potential for unresected RP disease depending on template Eggener et al, J Urol 2007; Carver et al, JCO 2007 MSKCC: improved clinical outcomes for low-stage and PC – RPLND since modified templates abandoned (independent variable) Stephenson et al, JCO 2005; Carver et al, JCO 2007





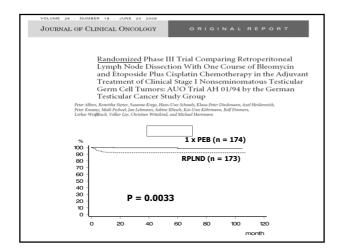
### Low Stage NSGCT RPLND: bilateral, nerve-sparing

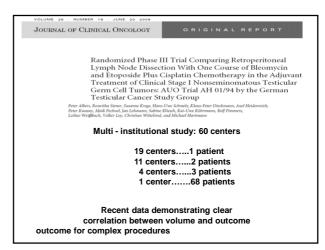
Performed with therapeutic intent: controlled RP... reduces chemotherapy burden (acute and long-term toxicity)

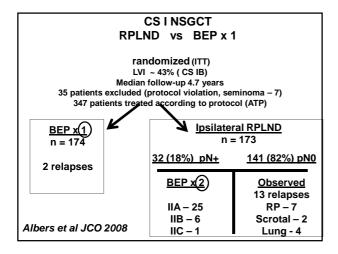
With more stringent selection criteria increased proportion of pathologic stage II with pN1 (rarely need chemotherapy)

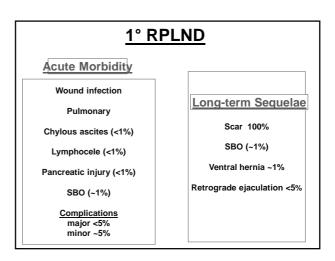
RP histology has remained constant (> 20% teratoma in pN+; 10% CS IB with unresected teratoma if observed or treated with CTX) and risk for late relapse

Significant decrease in systemic relapse rates(<10%) with improved selection criteria.... and bilateral RPLND



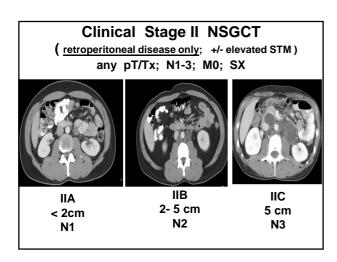






# Clinical Stage I NSGCT RPLND Advantages ↓ risk relapse ↓ risk of needing CTX removes teratoma ↓ risk late relapse No need for serial RP imaging Clinical Stage I NSGCT RPLND Disadvantages Overtreatment in (50% CS IB) ~ 10% - 20% receive postop CTX Adjuvant: ≥ pN2 (decreasing) Relapse (6%- 8%) Major surgery: acute/ long-term morbidity Retrograde ejaculation < 5% REQUIRES EXPERIENCED SURGEON

Clinical Stage II NSGCT Management following 1º RPLND				
Pathologic Stage	Criteria	Relapse rate (%)	Management	
pN0	All nodes -	<10%	Observe	
pN1	< 2cm <5 + nodes No ENE	10%-15%	Observe if compliant	
pN2/3	>2cm >6+ nodes ENE present ??	>40%	Adjuvant CTX preferable (B)EP x 2**	
**RPLND with therapeutic intent, post-op evaluation: NED				
If rising STM, new pulmonary nodule INDUCTION CHEMOTHERAPY				



Clinical Stage II NSGCT Chemotherapy or RPLND <u>as <i>initial therapy</i></u>				
Size of node(s) (Stage IIA, IIB, IIC)  Tumor marker (AFP / HCG) status (NADIR levels post-orchiectomy)  Unifocal vs multifocal adenopathy  Symptoms (back, flank pain)				
Which patients benefit from secondary (dual) therapy:  •Adjuvant chemotherapy after 1° RPLND  •PC-RPLND after chemotherapy				

	Clinical Stage II NSGCT <u>Initial</u> therapy		
Clinical stage	RPLND IIA selected IIB < 3 cm)	1 ° chemotherapy > 3 cm IIB all II C	
<u>markers</u>	negative	elevated	
# of nodes	single	multiple	
symptoms	absent	back/flank pain	

Clinical Stage II NSGCT			
Rationale for Primary RPLND			
Declining relapse rates and curative as single modality in most due to improved selection criteria			
Removes chemoresistant GCT, particularly TERATOMA (20% - 30%)			
More favorable long-term toxicity profile compared to chemotherapy			
Serial CT imaging of abdomen unnecessary in follow-up			
25% - 30% CS IIA are pN0			
Optimal patients for Primary RPLND: CS IIA, small, unifocal IIB (<3 cm); <u>NORMAL STM</u>			

Treatment and Outcome for Patients with <u>IIA and IIB</u> NSGCT				
	1989-1998	1999-2002		
Patients	181	71		
Treatment				
RPLND	113 (62%)	23 (32%)		
induction chemo	68 (38%)	48 (68%)		
5 year RFS %	84	98		
5 year DSS %	99	100		
Stephenson AJ et al JCO 2007; 25:5597-5602				

-	Improved Patient Selection Improved Clinical Outcomes CT imaging of Chest excluding patients with elevated STM excluding CS IIB >3cm
	Elevated STM (P < .0001), independent predictor of progression
	<u>Patients with elevated STM excluded</u> ; proportion of pN+:

- low-volume (pN1) disease increased by 24% (40% vs 64%)
- Progression-free survival improved from 83% to 96% (p = .005)
- Excluding patients with elevated STM from primary bilateral RPLND reduced extent of retroperitoneal disease and risk of relapse

Stephenson AJ et al, J Clin Oncol 2005; 23: 2781-8

### **Clinical Stage II NSGCT**

#### •all CS IIC

**Optimal patients for Induction Chemotherapy** 

• symptomatic, contralateral, multifocal, CS IIB >3 cm

Any CS II (A-C) with elevated STM

IGCCCG Risk Category					
	S Stage	LDH U/Liter	HCG (mIu/ml)	AFP (ng/ml)	
	S1	1-1.5 x ULN	<5,000	<1,000	
	S2	1.5-10 x ULN	5,000-50,000	1,000-10,000	
	S3	>10 x ULN	>50,000	>10,000	
		ULN= <u>U</u> pper <u>N</u> orm	Limit of I		
IGCCCG R	isk	CTX	Visceral	Mets	STM
Good	Е	P x 4; BEP x 3	3 pulmon	ary	S1
Intermedia	te	BEP x 4	non-pulm	onary	S2
Poor		BEP x 4	non-pulm	onary	S3

#### Clinical Stage II NSGCT Summary

Importance of patient selection:
 chemotherapy
 all IIC, multifocal; >3cm and /or symptomatic IIB
 any IIA/B/C with elevated and / or rising markers

IIA, <3cm unifocal, asymptomatic IIB

•Importance of optimal execution of selected treatment RPLND with curative intent
Chemotherapy appropriate regimen according to IGCCCCG criteria

\*Subset of patients require dual therapy (optimal sequencing) PC-RPLND all residual masses >1cm adjuvant chemotherapy after primary RPLND: pN2/3, noncompliant pN1

•Adjuvant chemotherapy (B)EP x 2

post op patient MUST be NED; if rising marker/ new nodule needs induction regimen

#### **Take Home Messages**

Delay in diagnosis continues to be a significant problem

A solid intratesticular solid mass is testicular cancer until proven

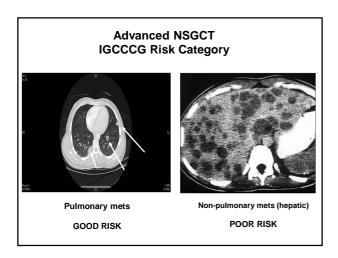
Scrotal sonography very useful: GCT's are usually hypoechoic, vascular lesion(s)

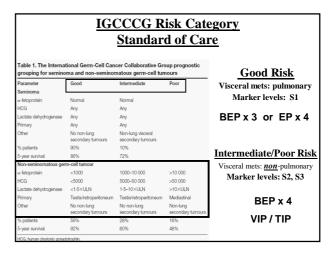
PET Scan has no role in initial evaluation of GCT

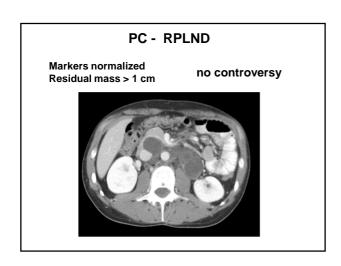
Elevated AFP excludes the diagnosis of seminoma despite histology of orchiectomy

Serum tumor markers that fail to normalize following orchiectomy usually reflect systemic disease and patients should receive 1° chemotherapy regardless of CT findings

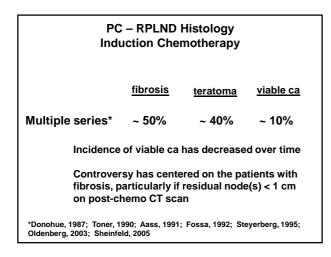
Bilateral nerve-sparing RPLND reduces risk of understaging and undertreating the retroperitoneum

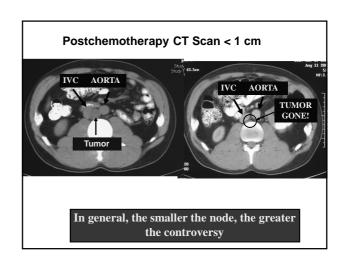






	PC-RPLND Histology			
Author, year	no.	<u>fibrosis</u>	teratoma	viable ca
Donohue, 1982	51	16 (31%)	16 (31%)	19 (37%)
Fossa, 1989	101	52 (51%)	37 (37%)	12 (12%)
Toner, 1990	122	57 (47%)	48 (38%)	17 (14%)
Aass,1991	173	85 (49%)	50 (25%)	38 (29%)
Steyerberg, 1995	556	250 (45%)	236 (42%)	70 13%)
Stenning,1998	153	45 (29%)	85 (56%)	23 (15%)
Hendry, 2002	330	84 (25%)	218 (66%)	28 (8%)
Oldenburg, 2003	87	58 (67%)	23 (26%)	6 (7%)
Carver, 2005	428	214 (50%)	183 (43%)	31 (7%)
TOTAL	2001	861 (43%)	896 (45%)	244 (12%)





## NSGCT Observation following Chemotherapy

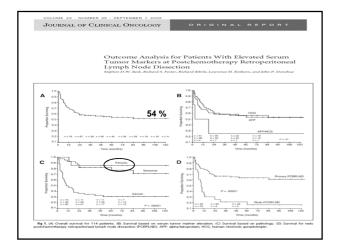
- 1) Assumption that surgery resulting in fibrosis is never therapeutic
- 2) Assumption that one can accurately predict fibrosis
- 3) Assumption that small foci of teratoma are "inert" or "benign"
- 4) Assumption that can achieve comparable patient outcomes with timely and appropriate treatment at relapse

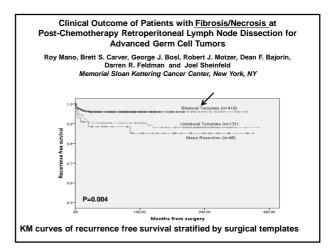
#### Therapeutic Benefit of a "Negative" PC-RPLND Pathologic Sample Error

Approximately 15% of patients will have a "negative" histology following PC-RPLND with elevated STM; yet ~ 90% will normalize their markers

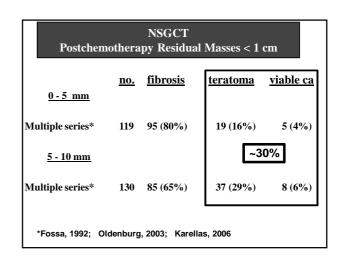
The more extensive a "negative" PC-RPLND, the less likelihood of relapse

Molecular data ??





# Residual mass < 1 cm Observation vs PC RPLND Most centers observe residual node(s) < 1 cm Risk of relapse: for < 1cm ~ 7%\*; for CR <5% PC RPLND\*\* < 1 cm; teratoma 25%, viable ca 5% < 0.5 cm; teratoma 16%; viable ca 4% \*IU, 2010 \*\*MSKCC, 2006



False negative

> 20%

#### Postchemotherapy Histology Steyerberg Model of Predicting Necrosis

• Sum score (necrosis):

-9.78 + 8.58 • "teratoma-negative"

+8.70 • "AFP Normal"

+7.61 • "HCG normal"

+9.69 • ln (LDH<sub>st</sub>)

-2.83 • Sqrt (postsize)

+0.147 • shrinkage

Steyerberg EW et al. J Clin Oncol 16:269, 1998

**Models Predicting Postchemotherapy Necrosis** 

Steyerberg EW et al; J Clin Oncol 1998 false negative > 20%

Albers P et al; J Urol 2004

accuracy 75%; sensitivity 52%; PPV 67%; NPV 77% "clinically irrelevant model"

Toner G et al; J Clin Oncol 1990 accuracy 83%

PC – RPLND: Teratoma in Retroperitoneum				
Teratoma in 1° YES	<u>no.</u>	Teratoma in RP		
Beck, 2004	375	321 (86%)		
Carver, 2006	224	150 (67%)		
Teratoma in 1° NO				
Toner, 1990	75	25 (33%)		
Beck, 2004	269	130 (48%)		
Carver, 2006	308	85 (28%)		
< 1 cm RP node	117	19 (16%)		
1 -2 cm RP node	120	25 (21%)		

Predicting teratoma in RP  Carver et al, JCO 2007					
	Hazard ratio	95% C.I.	P-value		
IGCCCG	0.61	0.35, 1.08	0.089		
2 <sup>nd</sup> line chemo	0.51	0.26, 1.0	0.048		
CT size pre-	0.77	0.7, 0.85	< 0.005		
CT size post-	1.6	1.4, 1.83	< 0.005		
ORCHIECTOMY					
teratoma	3.31	2.11, 5.21	< 0.005		
yolk sac	1.79	1.14, 2.83	0.012		
embryonal ca	1.41	0.8, 2.5	0.2		

#### Somatic-type Transformation of Teratoma: Higher incidence in <u>LR</u> and / or <u>Redo RPLND</u>

	no. pts	TMT (%)
1° RPLND	550	2 (0.4%)
PC - RPLND	532	18 (3%)
Redo RPLND	56	10 (18%)
Late Relapse	69	14 (20%)

ERMS
TERATOMA WITH SOMATIC-TYPE
TRANSFORMATION (2° somatic malignancy)

Unresected teratoma; some YS

Definition: Components of teratoma that histologically resemble a somatic malignancy. (e.g., PNET, enteric adenocarcinoma, rhabdomyosarcoma)

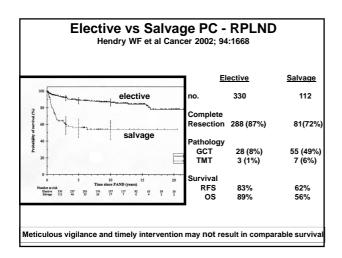
#### Somatic Transformation of Teratoma

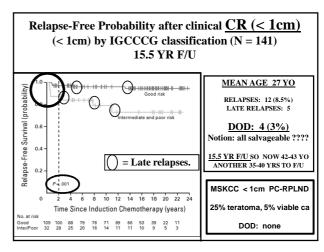
Definition: Components of teratoma that histologically resemble a somatic malignancy. (e.g., PNET, enteric adenocarcinoma, rhabdomyosarcoma)

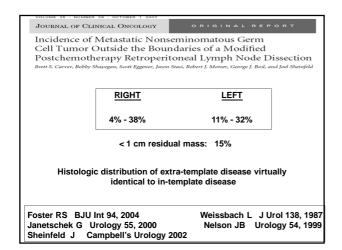
1° RPLND	0.4%
PC – RPLND	3%
Redo RPLND	18%
Late Relapse	20%

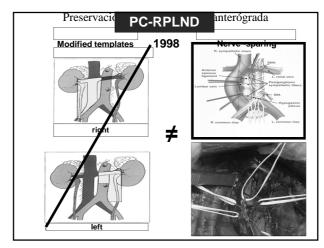
<u>LR</u>: 8-10X increased incidence compared to PC-RPLND ~12% in surveillance failures (no prior CTX)

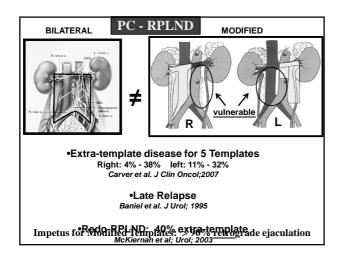
REDO RPLND: 6-8X increased incidence

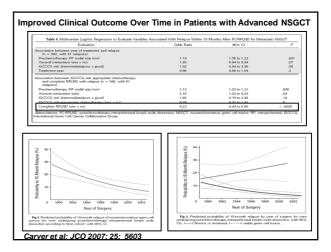


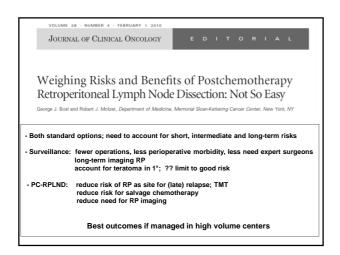


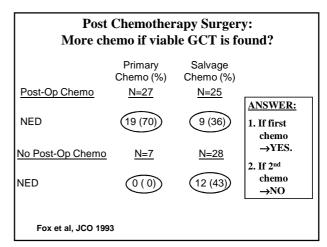


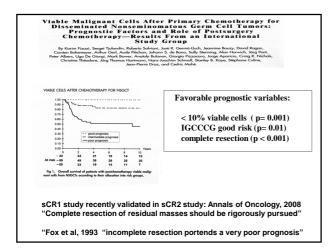


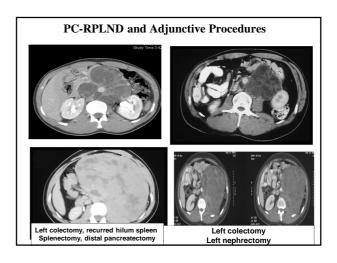


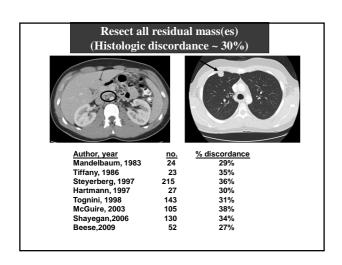








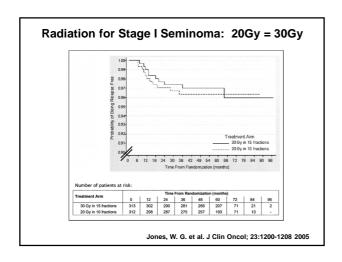




# SEMINOMA (B)EP is standard treatment for CS II B/C and CS III.

What about CS I and CS IIA

seminoma?



	PA-Strip Dog-Leg		P Value
	N=236	N = 242	
Relapses	9	9	NS
Pelvic Relapses	4 (2%)	0	0.04
RFS	96%	96.6%	NS
OS at 3-years	99.3%	100%	NS
No difference in F	RFS or OS but p	elvic relapses ↑	with PA-only.

#### Stage I – Radiation Considerations

- Relapse rate = 4%
- Dose
  - No benefit of 30Gy over 20Gy (Jones et al., JCO)
  - Standard is 20 25.5Gy

#### Port

- Dog-leg (DL) vs. Retroperitoneal-only (RP)
- No difference in overall relapse rate (4%) but higher pelvic relapse rate (2% vs. 0%). CT pelvis needed for RP-only port in f/u.
- No prophylactic mediastinal or left SCL XRT

#### Late toxicities

 Secondary malignancies (2-fold increase, esp. gastric, pancreatic, bladder, sigmoid, rectal, anal) but 50% outside radiation port (???)

### CS 1 Seminoma: XRT

 Stage
 RT
 Relapse (%)

 I
 20-25 Gy
 4%

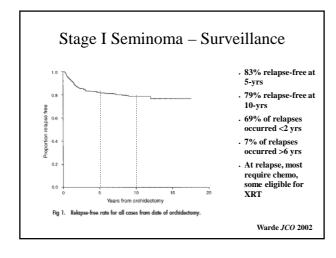
#### After RT, Increased cancer risk exists.

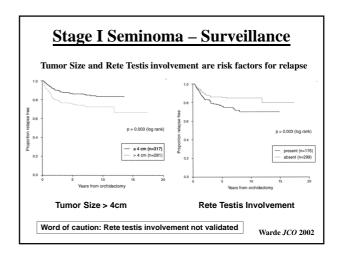
- 1. CA colon, stomach, pancreas, others.

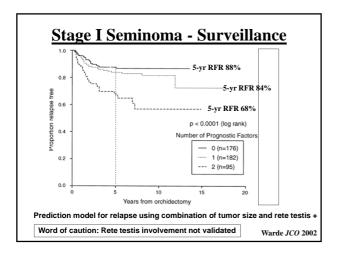
  Colon: RR 1.9; Pancreas: RR 3.8; Stomach: RR 4.1.
- 2. Long latency.

(Travis et al. JNCI 97: 1354, 2005)

Risk also increased after chemotherapy.







#### **Clinical Stage** I Seminoma

(http://www.nccn.org/professionals/physician\_gls/pdf/testicular.pdf)

1. <u>Surveillance</u>. Now recommended by most guidelines.

#### 2. Radiation Therapy—CS I.

Still in NCCN Guidelines. ~4-5% relapse.
\*\*Must discuss late cancer risks with patient.
Patients who relapse will receive BOTH
RT and Chemotherapy

- : Excess Combined Risk of Second Cancer + CVD.
  - 3. Risk Adapted Carboplatin.

Most don't need it. 85% cured after orchiectomy.

Carboplatii Oliver et al, Land		Seminoma er et al JCO, 2011
	RT	Carboplatin x 1
Patients	573	904
Relapse Free Rates	96%	94.7%
	TOXICITY	
Low platelets		
Gr 1-2 Gr 3-4	2% 0%	12% 4%
Lethargy/ Back to Work	20 Gy = Carbo	Carbo < 30 Gy

# Clinical Stage IIA/B(<3 cm) Seminoma

 Stage
 RT
 Relapse (%)

 IIA/B (<3 cm)</td>
 30 Gy
 10%-20%

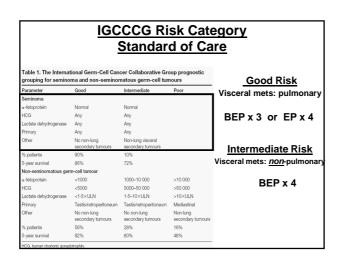
1. Radiation Therapy. Remains a standard of care.

HOWEVER, Must discuss late cancer risks. ~10%-20% relapse after RT

- :.Those who relapse will have had  $\underline{BOTH}$  Chemotherapy and RT  $\rightarrow$
- ∴ Excess <u>Combined</u> Risk of Second Cancer + Cardiovascular Disease.

Author	Stage	N	Relapse	
Mason (1988)	IIA/B	25	1 (4%)	
	IIC	24	6 (25%)	Radiation is a
Warde (1998)	IIA	40	4 (10%)	Standard of Car
	IIB	24	3 (13%)	3%) for Stage IIA and
	IIC	14	7 (50%)	small IIB (<3cm)
Patterson	IIA	46	6 (13%)	
(2001)	IIB	34	9 (26%)	
Zagars (2001)	IIA	6	0 (0%)	
	IIB	38	5 (13%)	Large Stage IIB
	IIC	25	3 (12%)	and Stage IIC
Classen (2003)	IIA	66	2 (3%)	Seminomas
	IIB	21	2 (10%)	Require
Chung (2004)	IIA	49	4 (8%)	Chemotherapy
	IIB	30	4 (13%)	
	IIC	16	10 (63%)	

IGCCCG Risk Groups for Seminoma <sup>1</sup>			
Risk Group	Features	5-yr OS	5-yr DFS
Good	No organ metastases other than lung	86%	82%
90%	( - NPVM)		
Intermediate			
	+ NPVM	72%	70%
10%			
NPVM = non-puli	monary visceral metastases		
NOTE: Mar	ker levels and primary sit	e <u>DON'T</u> affe	ect outcome
	·	¹IG0	CCCG, JCO, 199



#### **Conclusions**

GCT is highly curable.

Goal: Minimize toxicity--maintain high cure rate. Must remember and explain late toxicity.

Chemotherapy important but has toxicity.

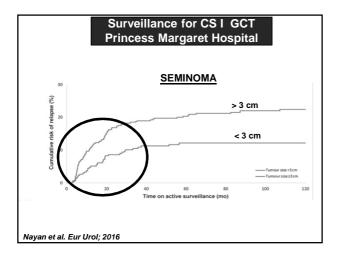
Teratoma always considered in NSGCT.

RPLND in NSGCT important - bilateral, nerve-sparing is best. Experience counts!

Careful patient selection at each stage.

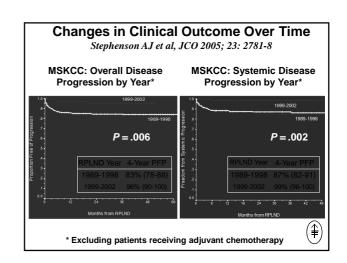
CS 2	VB Se	emin	oma:	NCCN Guidelines
	2.	CHE	MOT	HERAPY
Clin Stage	Total	Rel	DOD	Author
2A	20	0	0	Garcia-del-Muro, JCO 2008.
2B	72	6**	1	Giannis, J Cancer Res Clin Oncol 2009.
2A+2B	6+67	0	0	Tandstad, JCO 2011
**= ALL R				D ETOPOSIDE 400 mg/m <sup>2</sup> rior to 500)
1. CS 2	B relap	se rat	te lower	npo et al, Ann Oncol 2015) r for Chemo than RT. 4% in RT, 2% in CT.

	Stage I GCT Ac Time to	tive Surveillan Relapse	ce
	NSGCT LVI+	NSGCT LVI-	SEMINOMA
	n = 183	n = 935	n = 1,344
relapse	81 (44%)	132 (14%)	173 (13%)
<12 mo	73 (90%)	95 (72%)	73 (42%)
<24 mo	77 (95%)	118 (89%)	130 (75%)
<36 mo	79 (98%)	124 (93%)	160 92%)
>36 mo	2 (2%)	8 (7%)	14 (8%)
Kollmannsber	ger et al; JCO 33:51; 2014	1	



Ra	diation	for S	tage II Se	eminoma
Author	Stage	N	Relapse	
Mason (1988)	IIA/B	25	1 (4%)	
	IIC	24	6 (25%)	Radiation is a
Warde (1998)	IIA	40	4 (10%)	Standard of Care
	IIB	24	3 (13%)	for Stage IIA and
	IIC	14	7 (50%)	small IIB (<3cm)
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	IIB	21	2 (10%)	Require
Chung (2004)	IIA	49	4 (8%)	Chemotherapy
	IIB	30	4 (13%)	
	IIC	16	10 (63%)	

#### **CS I Seminoma: Carboplatin** (Aparacio et al, JCO, 2011) **Risk Factors** (unvalidated) 1. Tumor < 4 or > 4 cm 2. Rete Testis Invasion Present or Absent Risk Factors None Surveillance 5% 0 One Factor >4cm Rete Testis Carbo x2 **TOTAL** 7% 0 Median followup: 34 months



	0	ting teratoma in RP urver et al, JCO 2007		
	Hazard ratio	95% C.I.	P-value	
IGCCCG	0.61	0.35, 1.08	0.089	
2 <sup>nd</sup> line chemo	0.51	0.26, 1.0	0.048	
CT size pre-	0.77	0.7, 0.85	<0.005	
CT size post-	1.6	1.4, 1.83	< 0.005	
ORCHIECTOMY				
teratoma	3.31	2.11, 5.21	< 0.005	
yolk sac	1.79	1.14, 2.83	0.012	
embryonal ca	1.41	0.8, 2.5	0.2	

Late Relapse of Testicular Cancer
Definition

Most relapses in patients with low-stage and advanced
GCT occur within 2 years of treatment

Relapse following a 2 year disease-free interval

Absence of second primary GCT

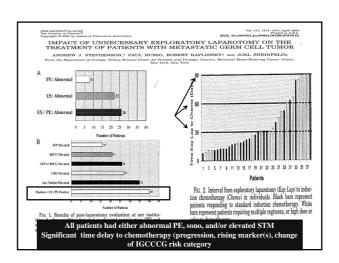
Incidence

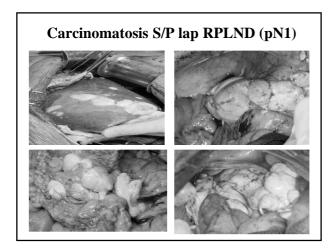
~ 3% - 4% and appears to be increasing

Oldenburg et al, JCO 2006; Oldenburg et al, Br J Cancer 2006

# Late Relapse of Testicular Cancer Clinical Features

- Distinct clinical entity
- •May occur at any time
- Chemoresistance
- •Retroperitoneum is the most common site
- Decreased survival <u>regardless of initial clinical stage</u>





#### Seminoma: Take home messages

#### Stage I

Survival 100%, relapse w/ size >4cm or rete testis + Surveillance least toxic, need better risk factors

- IIA → XRT (10% relapse rate) or Chemo (0% relapse)
  RPLND trial
  IIB → small/solitary chemo or XRT
  → large/multifocal = chemo

#### Advanced Disease

EPx4 (MSKCC) or BEPx3 (Indiana) for good-risk BEPx4 for intermediate-risk (NEVER POOR-RISK) Post-chemo PET and size criteria for resection More severe desmoplastic rxn post-chemo

	Clinical Stage I		
Pathologic Stage	Criteria	Relapse rate (%)	Management
pN0	All nodes -	<10%	Observe
pN1	< 2cm <5 + nodes No ENE	10%-15%	Observe if compliant
pN2/3	>2cm >6+ nodes ENE present ??	>40%	Adjuvant CTX preferable (B)EP x 2**
	with therapeutic inte		

#### **Clinical Stage II NSGCT** Summarv

•Importance of patient selection:

chemotherapy
all IIC, multifocal; >3cm and /or symptomatic IIB
any IIA/B/C with elevated and / or rising markers
RPLND

NORMAL markers
IIA, <3cm unifocal, asymptomatic IIB

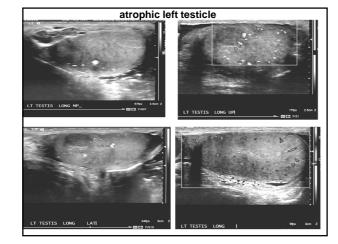
•Importance of optimal execution of selected treatment RPLND with curative intent

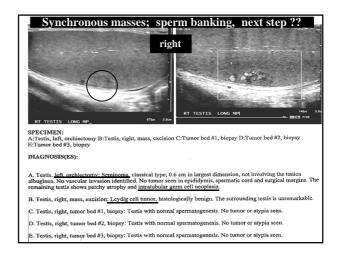
Chemotherapy appropriate regimen according to IGCCCCG criteria

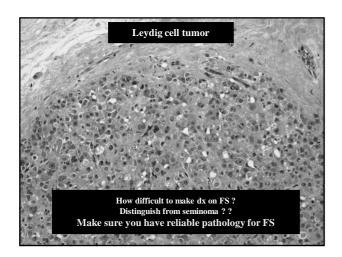
•Subset of patients require dual therapy (optimal sequencing) PC-RPLND all residual masses >1cm

adjuvant chemotherapy after primary RPLND: pN2/3, noncompliant pN1

Adjuvant chemotherapy (B)EP x 2
 post op patient MUST be NED;
 if rising marker/ new nodule needs induction regimen







#### **Testicular Tumors: Clinical Evaluation**

#### Required

History / Physical Exam Scrotal U/S (most RP primaries are testis in origin) Serum AFP, BHCG, LDH CXR

#### Only if clinically indicated

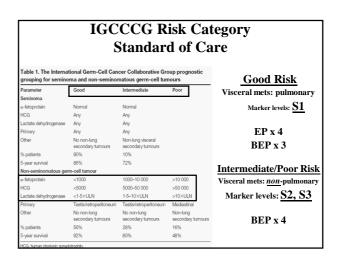
**PET scan:** (post - chemo seminoma )

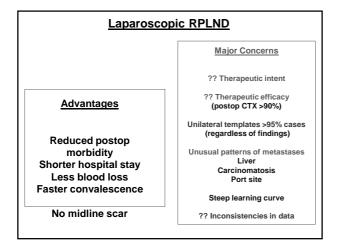
CT Chest, Abdomen, Pelvis

<u>no role in low-stage GCT</u>, no better accuracy over CT not capable of differentiating fibrosis from teratoma

MRI brain: pure chorio, neurologic symptoms

#### **Serum Tumor Markers IGCCCG Risk** Good Intermediate Poor Group S1S2S3AFP < 1000 1000-10,000 > 10,000 HCG 5000-50,000 < 5000 > 50,000 LDH 1.5-10x < 1.5x> 10x Chemotherapy BEPx3 BEPx3 BEPx3 EPx4 Chemotherapy regimen based on IGCCCG risk group Marker status (S1-3) based on post-orchiectomy nadir level





Stage I N	SGCT Active S Time to Relaps	
	IA	IB
	NSGCT LVI -	NSGCT LVI+
	n = 935	n = 183
relapse	132 (14%)	81 (44%)
<12 mo	95 (72%)	73 (90%)
<24 mo	118 (89%)	77 (95%)
<36 mo	124 (93%)	79 (98%)
>36 mo	8 (7%)	2 (2%)
Kollmannsberger et al;	JCO 33:51; 2014	

	SGCT Active Su Detection of Re			
	IA IB			
	NSGCT LVI-	NSGCT LVI+		
	n = 935	n = 183		
relapses	132 (14%)	81(44%)		
Method 1 <sup>st</sup> detection				
Abd CT	63 (48%)	31 (38%)		
markers	54 (41%)	49 (61%)		
N/A	12 (9%)			
Kollmannsberger et al;	JCO 33:51; 2014			

Sta	ige I GCT Act IGCCCG Risk	ive Surveillance of Relapses			
	NSGCT <u>LVI +</u> NSGCT <u>LVI -</u>				
	n = 183	n = 935			
relapses	81	132			
GCCCG risk					
Good	76 (94%)	116 (88%)			
Int	3 (4%)	13 (10%)			
Poor	2 (2%)	3 (2%)			
STATUS					
NED	79 (98%)	126 (95%)			
DOD		3 (2%)			
Rx death		2 (2%)			

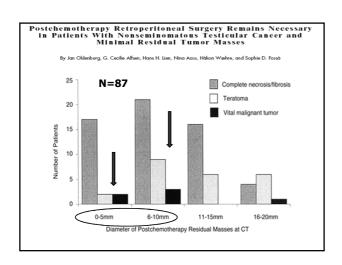
#### **RPLND**

- Once the decision is made to perform an RPLND, the surgeon should strive to maximize both the <u>staging</u> and <u>therapeutic</u> potential of the procedure. Bilateral templates accomplish this.
- Restricted templates unnecessarily increase probability of unresected RP metastasis; and despite effective cisplatinbased chemotherapy, the potential consequences include:

relapse, late relapse, re-operative RP surgery increased burden of treatment inferior clinical outcome in subset of patients

• Nerve-sparing techniques obviate the need for reduced templates

#### Stage I GCT Active Surveillance **Initial Detection of Relapses** SEMINOMA NSGCT LVI + NSGCT LVI n = 183 n = 935n = 1,34481 (44%) 132 (14%) 173 (13%) relapses Method 1st detection Abd CT 31 (38%) 63 (48%) 150 (87%) markers 49 (61%) 54 (41%) 6 (3%) N/A 12 (9%) 17 (10%) Kollmannsberger et al; JCO 33:51; 2014





# PENILE CANCER Update 2018

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Professor of Urology
The University of Texas
M. D. Anderson Cancer Center

#### Disclosure Statement

Advisory Role: Wolters Kluwer Publishing

#### PENILE CANCER Update 2018

- · Incidence, Risk Factors, Prevention
- . Management of the Primary Tumor
  - Organ Preserving Strategies
- · Management of the Inguinal Region
  - Clinical Node Negative
    - Minimally invasive staging
  - Clinically Positive nodes
    - Assessment
    - Adjuvant/Neoadjuvant therapy
    - InPACT Trial!

#### Penile Carcinoma Demographics

#### Incidence (1,2)

- <1 case per 100,000 US males
- 26,300 cases worldwide
- · 2-4 fold higher incidence
  - ◆ Cuba
  - ♦ Brazil
  - ◆ Columbia
  - ◆ Paraguay
  - ♦ India
- ◆ Thailand

#### Age @ Diagnosis (3)

- 55% ≤ 60
- 30% ≤ 50

(1) Parkin et al.: Cancer incidence in 5 continents Volume V: 19 (2) Parkin et al: Vaccine 24(Suppl 3):s3/11-25, 2006

# PENILE CARCINOMA Risk Factors

#### **Prior to Puberty**

- Lack of neonatal circumcision
- Poor hygiene
- Phimosis

Maden et al.: J. Natl. Cancer Inst., 85:199

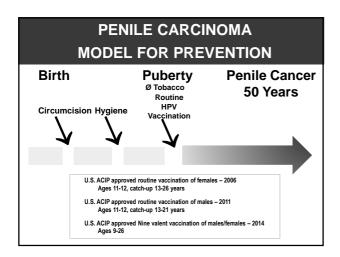
# PENILE CARCINOMA Risk Factors

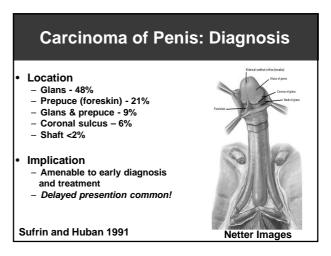
#### **After Puberty**

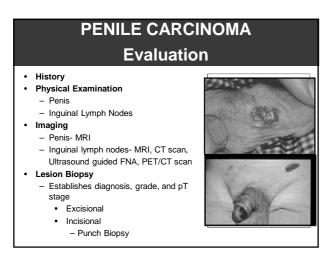
- Number of Sexual Partners
- HPV Infection
  - viral warts 6,11
  - Cancer 16,18,31,33,45,52,58
- Tobacco Products
  - Cigarette Smoke
  - Chewing Tobacco
  - Areca Nut (Snuff)
- Inflammation

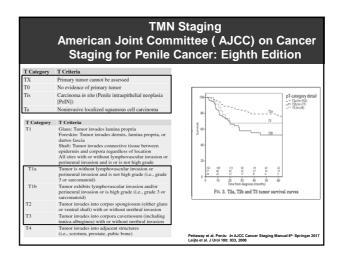
Maden et al.: J. Natl. Cancer Inst., 85:1993 Weiner et al.: Surg. Oncol. Clin N. Am., 4: 199 Harish et al.: Brit. J. Urol., 73: 1995 Micali et al.: Sex Trans Infect 77:2001

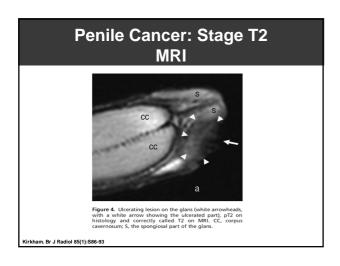
- Trauma, rash
- al: Sex Trans Infect 77:2001
  eet al Arch Dermatol 144: 591, 2008 Lichen Sclerosis

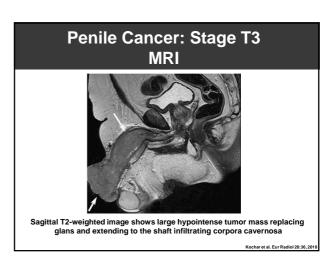












### **Penile Cancer** Natural History\* **Primary lesion** Dissemination Lymphatic +++ Hematogenous +/-Metastases (lungs, liver, bone, brain) Death → regional complications

#### **Penile Carcinoma Traditional Amputation**

- · Provides excellent local control
  - > Recurrence 0-8%
- Necessary in bulky Stage T2-T4
- Stratifies patient risk for Lymph node metastasis



vay CA et al: Tumors of the penis. In: Campbell-Walsh Urology, 9th ed. WB Saunders 2007; p 959. liningrat et al J Urol 192: 120, 2013

#### **Penile Amputation: The Problem**

- Young age @ Diagnosis<sup>(1)</sup>
   Median = 62 years
   43% < 60

  - 30% < 50
- Traditional Amputation Decreases Sexual Quality of Life<sup>(2)</sup>

   ↓ Erectile Function 8/18 (44%)

   ↓ Desire 6/18 (33%)

   ↓ Frequency 12/18 (66%)
  - Satisfaction 10/18 (55%)
- Regret(3)
  - 30% would choose penile preservation over longer survival
- Psychological well being/stress
   Impaired in up to 40% of patients
- Depressive symptoms in up to 31% of patients

#### **Penile Cancer Organ Preservation Strategies**

#### Goals

- Effective Local Control
- Organ Functionality
- Cosmetic Appearance



#### Penile Preservation: Observations<sup>(1)</sup>

- Agrawal performed partial or total amputations
  - Measured microscopic extent from gross margin
    - Grade I-II, only 13% extended to 5mm
    - Grade III, 41% to 5mm, 25% extended to 10mm
  - "2 cm tumor free"margin not supported!

(1) Agrawal et al., Brit J Urol 85:299, 2000 – 64 patients, Clinical Stage ≥ T2 No skip lesions noted. Recommend: 10 mm margin Grades 1-2, 15 mm margin Grade 3

#### **Penile Carcinoma Organ Preservation Strategies: Selection**

- Optimal Tumors
  - Tis, Ta, T1 Grade 1-2
    - · Easier to obtain local control
    - Metastatic rates 0 10%
    - Procedures
      - >Glans resurfacing
      - **≻Laser ablation**
      - >Excisions/reconstruction
- Select Tumors
  - Distal T2, Low grade
    - Procedures
      - ➤ Glans sparing excisions
      - ➤ Glansectomy with reconstruction

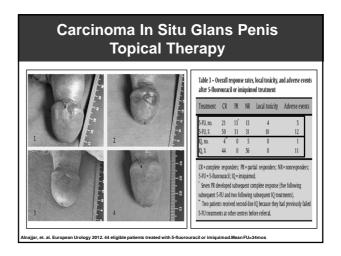


# Penile Carcinoma In Situ Treatment Options

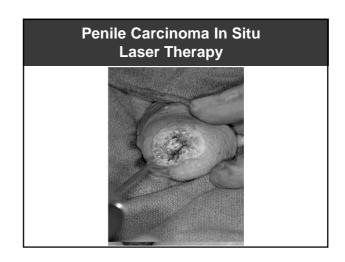
- Surgical Excision
  - 5 mm margin, underlying tissue
  - Glans resurfacing
- Laser
- CO<sub>2</sub>, Neodymium:YAG, KTP
- Moh's Excision
- Pathologic expertise, facilities
- · Topical therapy
  - 5 Flourouracil
  - Imiquimod

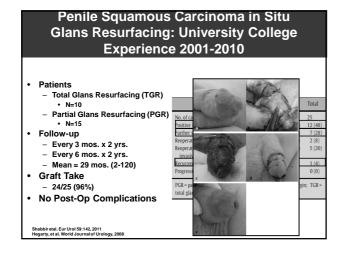




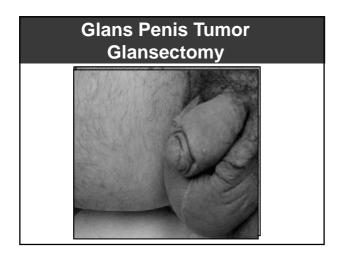


#### Penile Carcinoma In Situ **Laser Therapy** Treated Area Series Cancer Premalignant No. Local Mean Patients Recurrence Follow-Number (%) ups (mos) Van Yes No 19 5 (26) 25 Bezooijen<sup>(1)</sup> Meijer<sup>(2)</sup> Yes No 4 (67) 38 Teitjen<sup>(3)</sup> Yes Yes\* 12 1 (8) 58 1 (6) 47 15% Acetic Acid used to treat additional areas. 10 J Urol 166:1670, 2001. Noodymium: YAG or C0, Laser, mean follow-up = 25 mos. 10 Urology 82:593, 2007. Noodymium: YAG Laser, mean follow-up = 38 mos. 10 Urology 32:593, 1998. C0s, KTP. Neodymium: YAG, mean follow-up = 58 mos. 10 JUrol 168:2418, 2002. Noodymium: YAG Laser, mean follow-up = 47 mos.

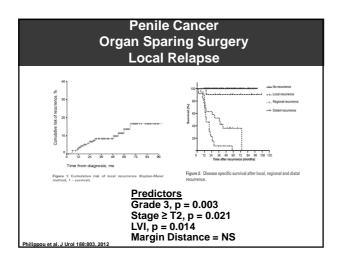


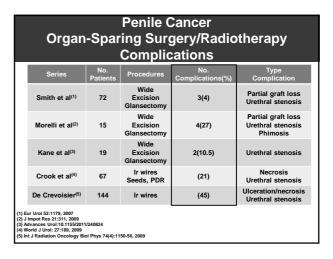






Penile Cancer Organ-Sparing Surgery							
Series	No. Patients	Procedures		largin Status Pos	Distance To Margin (%)	Incidence Recurrence (%)	Follow-Up
Minhas et al.(1) UK	51	Wide Excision Glansectomy	51	•	0-10mm (48) 0<20mm (90)	2 (4) 2 (6) (3)	26 medium
Smith et al.(2) UK	72	Wide Excision Glansectomy	55	6	0-5mm (61) ≥6mm (39)	3 (4)	27 mean
Morelli et al.(3) Italy	17	Wide Excision Glansectomy	15		NS	0	36 mean
Kane et al. <sup>(4)</sup> Ireland	19	Wide Excision Glansectomy		NS	NS	1 (5)	26 mean
Li et al. <sup>(5)</sup> China	32	Wide Excision Extended Circumcision	32	-	NS	3 (9)	26.5 median
Feldman et al.(6) USA	56	Excision, partial glansectomy, topical	42	14	NS	12 (21)	5 years median
Philippou et al. <sup>(7)</sup> UK	179	CIRC, WLE glansectomy, glansectomy, distal corporectomy	167	12	5mm (mean)	16 (8.9)	43 mean
Philippou et al. (*) UK  BJU Int 96:1040, 2005  Eur Urol 56:1779, 2007  Int J Impot Res 21:311, 20  Advances Urol doi10.1155	09	glansectomy, glansectomy, distal corporectomy  (5) Urole (6) J Urol	ogy 28: ol 186:1	1121, 2011	omm (mean)	16	(8.9)





# Penile Carcinoma Organ Preserving Strategies

- Feasible in Stage Ta, T1, Tis T1, Small T2
- Sexual QOL
  - Favorable Laser, limited excisions
  - Additional studies required
- Complication rates
  - Surgery low
  - Radiation low moderate
- Higher incidence local recurrence
  - Survival was not adversely impacted
  - Achieving negative margins important
  - Careful long-term follow-up required!
    - Early biopsy for suspicious lesions.

#### Penile Cancer Requirements for Surgical <u>Cure(1-10)</u>

- · Limited unilateral inguinal metastases
  - 1-2 unilateral nodes,> 70% 5 year disease free survival
- ≥ 3 unilateral or bilateral metastases
  - 12 60% 5 year disease free survival
- Extranodal cancer extension
  - 5 6% 5 year disease free survival
- · Pelvic lymph node metastases

10% 5 year survival

P Srinivas et al.: J Urol 137:1987

Srinivas et al.: J Urol 137:1987

(9) Johnson et al.: Urol 24:198 (10) Li et al. Br. J Cancer 2015 deKernion et al.: Cancer 32:1973
 Powsang et al: Semin Surg Oncol 6:1990
 (8) Reddy et al: BJUI IN PRESS

# Penile Cancer Inguinal Lymph Node Dissection (ILND)/Staging Procedure

#### Indicated:

Patients with palpable inguinal adenopathy

#### Advised:

- Patients with no palpable lymph nodes
  - NCCN,EAU guidelines favor early Staging/ILND among select patients

Hakenberg et al Eur Urol 67:142, 2015 NCCN Clinical Practice Guidelines 2016

T Criteria	Stage	pN+	Risk
Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades connective tissue between	<u>≤ T1a</u>	0-18%	Low
epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade	T1b	33-50%	High
Tumor is without lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid)	T2	33-35%	High
Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid)	T3-T4	49-53%	High
Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion			
Tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion			al stagin
Tumor invades into adjacent structures (i.e., scrotum, prostate, pubic bone)		·	commend
	T Criteria Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is not is not high grade Tumor is without lymphovascular invasion or, gerineural invasion and is not high grade (i.e., grade 3 or sarcomatoid) Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid) Tumor invades into corpor cavernosum (including tunica albuginea) with or without urethral invasion Tumor invades into corpora cavernosum (including tunica albuginea) with or without urethral invasion Tumor invades into corpora cavernosum (including tunica into grant introduces)	T Criteria Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades dermis, lamina propria, or dartos fascia Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is or is not high grade Tumor exhibits lymphovascular invasion or perineural invasion and is not high grade (i.e., grade 3 or sarcomatoid) Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid) Tumor invades into corpus spongiosum (either glans or ventral shaft) with or without urethral invasion Tumor invades into corpora cavernosum (including tumor invades into corpora cavernosum (including tumor invades into corpora cavernosum (including tumor invades into edipcent structures (i.e. servium prostate nuthic boxels)	Glans: Tumor invades lamina propria Foreskin: Tumor invades dermis, lamina propria, or dartos fascia. Shaft: Tumor invades connective tissue between epidermis and corpora regardless of location All sites with or without lymphovascular invasion or perineural invasion and is no ris hot high grade Tumor is without lymphovascular invasion or perineural invasion and is no thigh grade (i.e., grade 3 or sarcomatoid) Tumor exhibits lymphovascular invasion and/or perineural invasion or is high grade (i.e., grade 3 or sarcomatoid) Tumor invades into corpors spongiosum (either glans or ventral shaft) with or without urethral invasion Tumor invades into corpora cavernosum (including tunic albuginea) with or without urethral invasion Tumor invades into adjacent structures

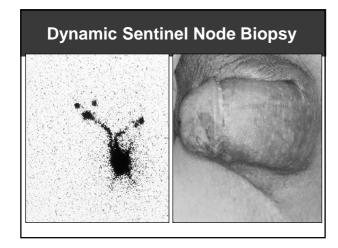
# PENILE CANCER STAGING STRATEGIES TO MINIMIZE MORBIDITY

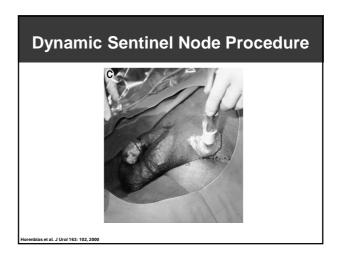
- Sentinel or extended lymph node biopsy (SLNB)<sup>(1,2)</sup>
- Dynamic Sentinel node Biopsy<sup>(3)</sup>
- Superficial/modified dissections(4,5)
- Lap/Robotic Lymphadenectomy(6-7)

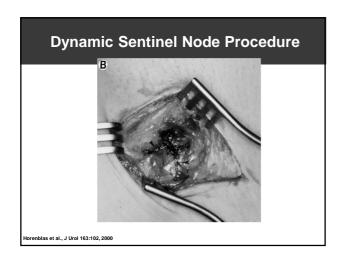
Cabanas: Cancer, 39:1977
 Pettaway: J Urol, 154:1995
 Horenblas: J Urol:163:2000
 Catalona: J Urol, 140, 1988
 Spiess: J Urol, 177, 2007
 Tobias-Machado: J Endo Urol 22, 2008
 Watin et al. B.IIII 2013

# Dynamic Sentinel Lymph Node Biopsy Goal

To determine where in the inguinal lymph node field the "sentinel" node resides in the individual patient.







#### **Dynamic Sentinel Lymph** Node Biopsy (DSNB): Modified Technique<sup>(1)</sup> **Results From High Volume Centers**

Series No	. Patients	No. Groins Metastases	DSNB Detected Metastase Number (%)	Follow-up (mos) es Median
Leijte, et al.(2)	58	21	20/21 (95)	30
Hadway, et al.(3	75	22	21/22 (95)	11
Leijte, et al.(4)	323	85	79/85 (93)*	18
Kirrander et al	5) 57	13	11/13 (85)*	21

(3) BJU Int 100:561, 2007

(4) J Clin Oncol:27(20):3325, 2009- \*On follow-up 4/6

(5) BJU Int 111:48-53 2013-\*On follow-up 2 patients with false negative DSNB died of disease

#### **Penile Carcinoma Superficial Inguinal** Lymph Node Dissection(1-4)

- Removes nodal tissue above fascia lata
- Frozen section
- Limited morbidity Identifies "First Echelon" lymph nodes
- **Spares Saphenous Vein**
- Rare inguinal recurrences!



as et al., J. Urol., 167:1638, 2002 I., J. Urol., 153: 246A, 1995 et al., J. Urol., 153:246A, 1995 1 Urol 177:2157,2007- No recurre

#### Complications of DSNB, Laparascopic Modified / Superficial Inguinal Lymphadenectomy

Study	Surgical Approach	#Complications/ #Groins	†Complication Rate (%	
Kroon, et al.(1)	DSNB	14/189	7	
Tobias-Machado, et al.(2)	Laparoscopic	2/10	20	
Sotelo, et al.(3)	Laparoscopic	3/14	21	
Bouchot, et al.(4)	Modified	12/118	12	
Bevan-Thomas, et al.(5)	Superficial	23/66	35	
Spiess, et al.(6)	Superficial	15/52*	29	

(1) J Urol 173:813, 2005 (2) J Urol 177:953, 2007 (3) J End Urol 21:364, 2007 (6) World J Urol; 27:205

#### Inquinal STAGING: No Palpable Adenopathy- Contemporary Strategies

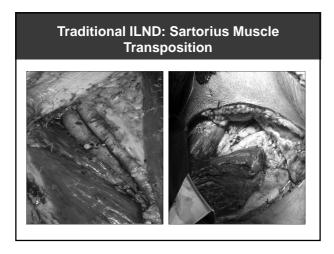
- Dynamic Sentinel Node Biopsy
  - NCCN, EAU guidelines
- Superficial/modified dissections
  - NCCN, EAU guidelines
- Lap/Robotic Lymphadenectomy
  - Option at experienced centers

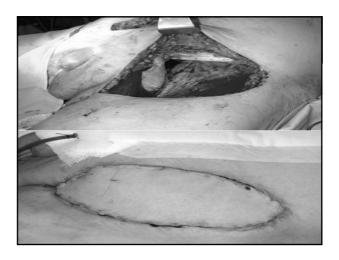
al. J Natl Comp Canc Net 11:659,2013; Pizzocaro et al. 57:1002, 2010; Horenblas: J Urol:163:2000; Catalona: J Urol, 140, 1988; J Urol, 177, 2007; Tobias-Machado: J Endo Urol 22, 2008; Master J Urol 188: 1176, 2012; Schwentner et al J Endourol 27:497, 2013

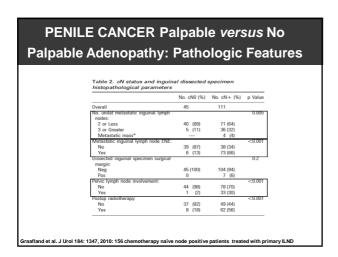
#### Penile Carcinoma: Traditional Inguinal/ Ilioinguinal Lymphadenectomy

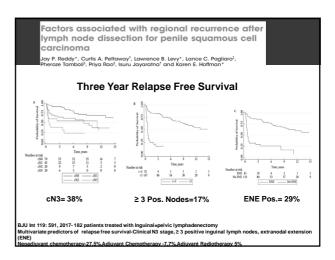
- **Proven Metastasis** 
  - Efficacy justifies morbidity
- Goals
  - Eradicate all cancer
  - Adjuvant therapy candidate
  - Technical
    - ♦ Cover exposed vasculature
    - ♦ Provide for rapid wound healing









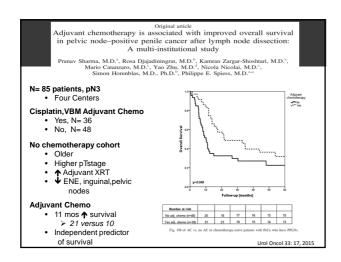


# PENILE CANCER Adjuvant Strategies Post Lymphadenectomy

- Radiation
- Chemotherapy

How should these strategies be integrated to improve survival?

#### **VULVAR CANCER** Ilioinguinal Versus Inguinal Dissection and XRT Randomized Trial: Gynecologic Oncology Group **Randomized Patients** 59 Inguinal Dissection and XRT 54, Inguinal and Pelvic Dissection **Treatment Groups** - Prognostic Factor Equal XRT - Bilateral Groins and Pelvis • 4500-5000 RAD **Groin Recurrence** - XRT = 5.1% - Surgery = 23.6% Pelvic/Local Recurrence No difference



Penile Cancer Guidelines:Adjuvant Therapy
High Risk Post Inguinal Lymphadenectomy

NCCN 1

PN2-3

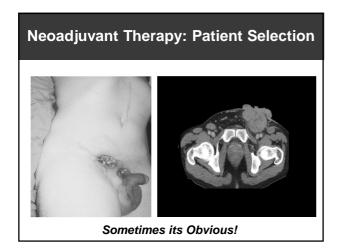
Radiation , Chemo-radiation or Chemotherapy

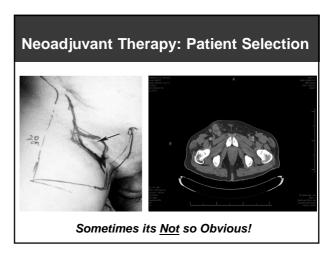
EAU 2

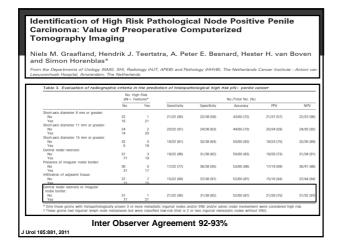
PN2-N3

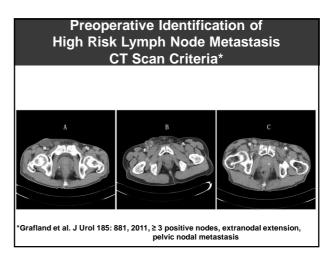
Chemotherapy

NCCN Clinical Practice Guidelines 2016
Hakenberg et al. Eur Urol 67: 2015



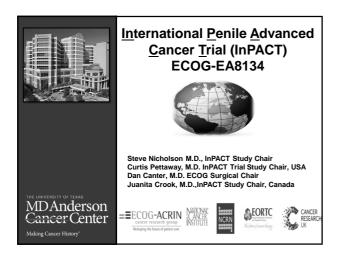






#### **Chemotherapy for Advanced Penile Squamous Carcinoma** Objective Median Response Survival No. No. (%) **Series** Regimen Pts. Months Nicholson (1) 10 (38.5) T,P,F 26 7.7 (NS) Djajadiningrat (2) T,P,F 11 (44) 10 (6.7-28.1) 26 Pagliaro (3) T,I,P 30 15 (50) 17 (10-60+)

# Overall Survival according to TIP Chemotherapy Response @ 5 years Chemotherapy Response @ 50 years Chemotherapy With Chemotherapy with Curative Intent & 50 years Chemotherapy with Curative Intent Response with Chemotherapy with Curative Intent & 50 years Chemotherapy with Curative Intent & 50 years



(\*\*IBJC 109: 2554, 2013- patient s with advanced regional or distant metastatic pe docetaxel, cisplatin, 5 Flourouracil chemotherapy (\*\*) Clin Genitouri, Gancer 13:44, 2015 - advanced regional metastases (\*\*IBJC 10:10 Clin Chemotherapy (\*\*) Clin Oncol 28: 3851,2010-advanced regional metastases treated with paclitaxe

# InPACT Trial: Important Questions

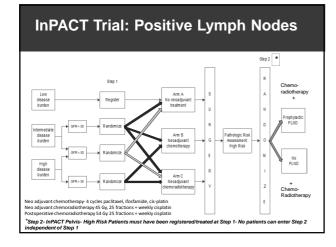
#### Question #1-InPACT Neoadjuvant

- a) What is the role of neoadjuvant therapy?
- b) Does either chemotherapy or chemoradiation provide superior outcomes?

#### Question #2- InPACT Pelvis

Among patients with prior ILND and adverse features receiving chemoradiation what is the role of prophylactic PLND?

- ≥ 3 positive nodes, extranodal extension
- Bilateral metastases



#### InPACT Trial: North American Accrual Goal

#### Targe

- 200 patients USA, Canada
  - ECOG, SWOG, Alliance, NRG,NCIC
- 400 Total

#### **Primary Endpoint**

Survival

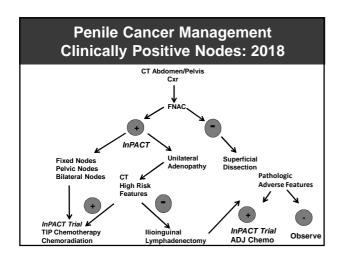
#### Secondary endpoint

- DSS, DFS,DMFS,LRFS,pN0
- Toxicity
- Surgical complications
- QOL
- Feasibility of delivering treatment

#### InPACT Trial Information

>http://ecog-acrin.org/clinical-trials/ea8134-educational-materials







#### **Urethral Carcinoma:** Update 2018

Curtis A. Pettaway, M. D. **Professor Department of Urology** The University of Texas M. D. Anderson Cancer Center

#### Disclosure Statement

· Advisory Role: Wolters Kluwer Publishing

#### **Urethral Carcinoma: Update 2018**

- > Disease presentation in Males & Females
  - · Incidence, Risk Factors, Location, Histologic types
- > Evaluation, Staging & Natural History
  - MRI
- > Treatment & Prognosis-Males & Females
  - Location
  - Stage
    - Multimodal Strategies in Advanced disease

#### **Urethral Carcinoma**(1-3)

- Incidence (1)
  - 1973-2002, approx. 1615 cases
  - Males-4.3/million
  - Females- 1.5/million
  - Increases with age
- Age (2,3)
  - Males 59 (36-92)
  - Females 60 (21-84)
- Racial Predisposition (1)
  - More common among African Americans

#### **Urethral Carcinoma Associated Factors**

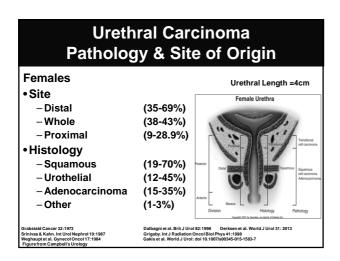
- Male
  - Stricture (25-76%)
  - Sexually transmitted disease (24-50%)
  - HPV infection (29%)
  - Trauma (7%)
- Female
  - Chronic irritation (caruncles, fibrosis, polyps, HPV infection)

  - Sexual activity - Diverticula

#### Inflammation is a common theme

ology 53:1999 cer Res 52: 1992, Derksen et al. World J Urol 31:2013

#### **Urethral Carcinoma** Pathology & Site of Origin Males Urethral Length = 20cm Site - Bulbo membranous (25-59%)- Anterior (33-39%)- Prostatic **(7%-**38%) Pathologic types Squamous (63-80%) Urothelial (20-33%) - Adenocarcinoma (<5%) - Other (<u><</u>2%)

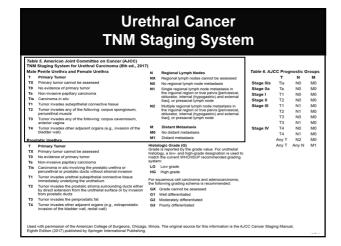


#### **Urethral Carcinoma Clinical Manifestations** Male 43% Obstruction **Irritative Symptoms** 20% Hematuria 17% 28% Mass 20% **Abscess** 4% Discharge Incidental 4% Median Time to Presentation - 7.5 mos

#### **Urethral Carcinoma Clinical Manifestations Female** 41% **Irritative Spotting** 35% Obstructive 28% Hematuria 23% Mass 20% **Discomfort** 13% Discharge 7% Incidental 2% Median Time to Presentation - 4.5 mos ni et al. Brit J Urol 82: 1998 72 patients 1958-1994

# Urethral Carcinoma Evaluation Examination Genitalia Protruding lesions Prolapse, caruncles, benign or maligant tumors Palpable Masses Diverticuli, abscess, tumors Inguinal Examination Palpable adenopathy usually related to metastasis Cystourethroscopy with biopsy, vaginoscopy Multiple sites along urethra Exam under anesthesia MRI to define soft tissue detail CT scan abdomen, CXR

Male Urethral CA-LJ Pretherapy



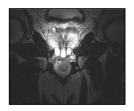
# Sagittal T2 weighted image with tumor involving the corpus spongiosum.

 The prostatic urethra is dilated (yellow)



# MALE URETHRAL CA- LJ Pretherapy- Stage T3?

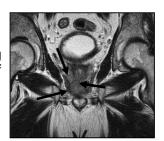
 Coronal T2 weighted images. Tumor involves the corpus spongiosum. Superior border of the bulb (and hence UGD is likely) involved.





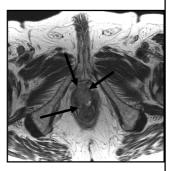
### MALE URETHRAL CA-CN Pretreatment Stage T4

 T2 weighted Coronal image shows mass (yellow) extending to the right side of the prostate gland and involving the right levator anus muscle (white).



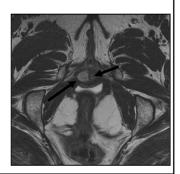
## MALE URETHRAL CA-CN Pretreatment Stage T4

 T2 weighted Coronal image above the level of the UG diaphragm shows mass (yellow) extending posterior to involve the anterior wall of the rectum (white)



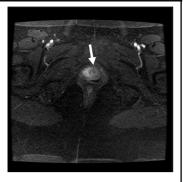
#### Female Urethral - CA Pretreatment - LJ

- Axial T2. Vagina distended with gel.
- Urethra (yellow)
- Tumor in diverticulum (white)



#### **FEMALE URETHRAL CA-LJ**

- Axial T1 post contrast
- Tumor enhancing (yellow)

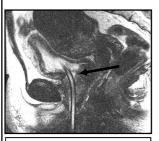


#### Female Urethral CA-LJ Stage T2

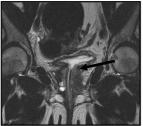
- Sagittal T2.
   Tumor in distal urethra (yellow)
- Vagina and bladder wall not involved



#### **Female Urethral CA-BB Pretreatment Stage T3**



Sagittal T2. Mass in urethra involving bladder neck



Coronal T2. Mass involving bladder neck

#### **Urethral Carcinoma Natural History**

#### **Primary Tumor**

- · Local growth and extension
  - Males
    - Corpus spongiosum,cavernosum
    - GU Diaphragm, levator muscles, prostate, scrotum, rectum
  - Females
    - Corpus Spongiosum, vagina, bladder
    - Levator muscles

#### **Urethral Carcinoma Natural History**

#### Metastasis

- · Regional Lymph Nodes @ Presentation
  - Males (14-30%)
  - Females (21-28%)
  - Distal, pendulous tumors→Inguinal nodes
  - Proximal, bulbomembranous tumors→Pelvic Nodes
- Distant Metastases
  - @ presentation (rare, 0-19%)
  - Post-therapy recurrence (30-40%)
    - · Lung, liver, bone, lymph nodes, brain

nary Cancer Surgery, Lea & Febiger, Phila

#### **Male Urethral Carcinoma Treatment & Prognostic Factors**

#### **Determine Treatment**

- Stage
- Location
- Histology

#### **Prognostic Factors**

Stage, Grade, Surgery versus none

Dinney et al Urology 43: 1994

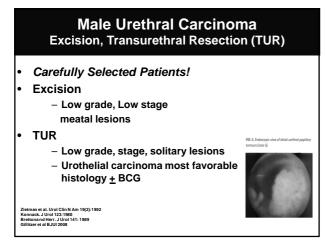
Rabbani et al Cancer 117: 2011 SEER Data 5,10 year Cancer specific survival N=2,065 patients

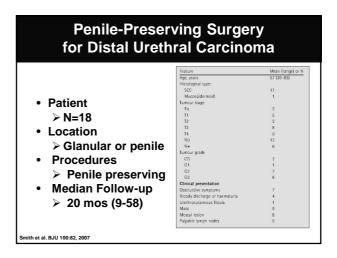
#### **Male Urethral Carcinoma** Survival According to Location<sup>(1)</sup>

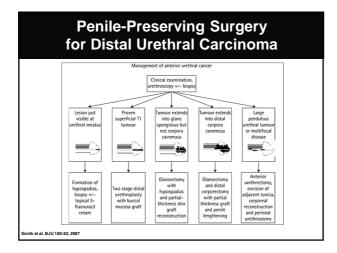
Urethral Location	No. Patients		Stag	es D1-D2	Incidence Local Relapse (%)	Disease Specific Survival (%) (mos)	Mean F/U (mos)
Fossa	4(2)	3		1	0	100	93
Penile	11 <sup>(3)</sup>	1	3	7	1/7 (14)	60	48
Bulbo- membranous	7 <sup>(4)</sup>	2	2	4	4/7 (57)	29	31

#### **Male Urethral Carcinoma Treatment Options**

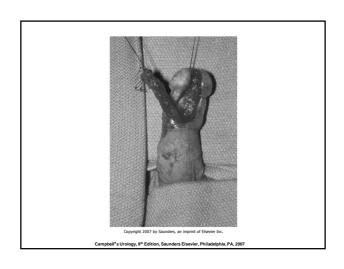
- **Anterior Urethra** 
  - Transurethral resection/fulguration
  - Excisions, penile conserving procedures
  - Partial or total penectomy
- **Posterior Urethra** 
  - Transurethral resection carefully selected patients
  - Exenterative surgery
  - Multi-modal therapy favored

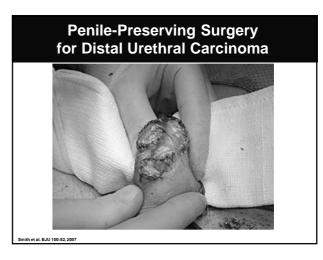


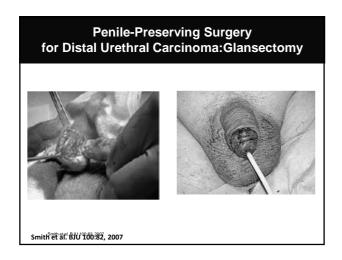


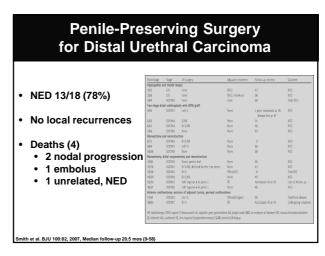




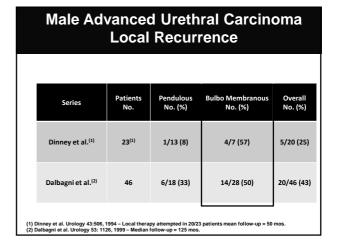


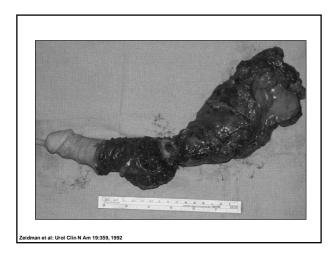


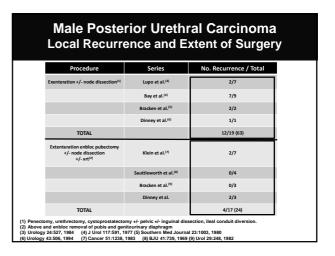




			Su	rviv	/al (	%)			
Series	Year	Sta		n\/aluo	Locatio	n  Proximal	n\/alua		ollow-up I(mos)
Dinney et al.					60	29	NS	52 <sup>(7)</sup>	50(4)
Dalbagni et a	l <sup>(2)</sup> 1958-96	83	36	0.07	69	26	0.03	42(8)	125
Thyaviljalry <sup>(3)</sup> et al.	1988-2001	67	33	0.001	72	36	0.02	49(8)	48
1) Urolory 43(4):5 2) Urology 53:113 3 Int J Urology 53:144 4) Mean Follow-u 5 Stages A-B 5 Stages C-D 7) Disease Specif 6) Overall Survivs	66, 1999 6, 2006 p								







# Male Urethral Carcinoma Radiation Therapy

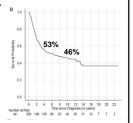
- Poor Local Control
  - Anterior tumors, 0-25% five year survival
  - Posterior tumors only anecdotal survivors
- Complications
  - Stricture
  - Chronic Edema
  - Necrosis
  - Fistula

Kaplan et al. J Urol 98:1967 Hopkins & Grabstald: Campbell's Urology. W.B. Saunders, 19i Zietman et al. Urol Clin N Am 19:1992 Dalbagni et al. Urology 53:1126,1999 Bracken et al. Southern Med Journal 73:1003,1980

# Female Urethral Carcinoma Treatment and Prognostic Factors

#### **Determine Treatment**

- Stage
- Location
- Histology



#### **Prognostic Factors**

>Age, Race, Stage,

Histology, Size, Surgery versus None

rigsby. Int J Radiat Oncol Biol Phys 41:1998; Champ et al. Urology 80: 2012- SEER Data 5,10 year Cause specific surviv L=722 patients ;Dalbagni et al. Brit J Urol 82:1998; Garden et al. cancer 71:1993; Brackent et al. J Urol 116:1976 Blosswiet al. Radiotheraw and Decology 65:2000

# Female Urethral Carcinoma Treatment Options

#### Tis, T1, Small T2

- · Transurethral resection
- Distal urethrectomy
- · Radiation therapy

#### T2-T4

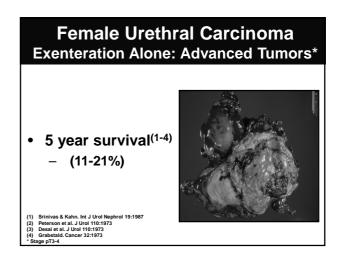
- Exenterative surgery
- Radiation
- Multimodal therapy favored

#### **Female Urethral Carcinoma** Surgery + Radiotherapy: Low Stage Tumors(1) Follow-Up Period No. Pts. Series Survival (%) Treatment 1/3 (33) 8/10 (80) 20/24 (83) NS (80) Surgery (2) Bracken et al. (4) 96 months Grabstald (5) Herr (6) DiMarco(9) 5 years 5 years 5 years 24 27 Surgery + XRT (3) 5/8 (63) 2/3 (67) 1 (100) 1 (100) Bracken et al. (4) 53 months 8 3 1 1 Grabstald <sup>(5)</sup> Hahn <sup>(7)</sup> Ali <sup>(8)</sup> 5 years 5 years 48 months AVF 38/50 (76) (5) Cancer 32: 1973 (6) Campbell's Urol (7) Urology 37: 1991 (8) Cancer 62: 1988 Surgery and Adjuvant R J Urol 116: 1976 Urologic Oncol 22: 2004

#### **Female Urethral Carcinoma** Low Stage: Radiotherapy<sup>(1)</sup> 5- Year Survival (%) No. Patients Series Treatment Grabstald (1) Delclos(2) XRT + Implant XRT + Implant XRT + Implant Delclos<sup>(2)</sup> Taggart<sup>(3)</sup> Johnson & O' Connell<sup>(4)</sup> Chu<sup>(5)</sup> 6/11 8/15 (55) (53)<sup>(3)</sup> 11 15 XRT + Implant (60)<sup>(4)</sup> (64) (77) (77)<sup>(7)</sup> (100) 3/8 7/11 5 11 Weghaupt<sup>(6)</sup> Pointon<sup>(7)</sup> Prempree<sup>(8)</sup> 30/42 20/26 6/6 8/8 Antoniades<sup>(9)</sup> Milosevic<sup>(10)</sup> Implant Alone XRT + Implant (100)<sup>(9)</sup> (71)<sup>(10)</sup> 101/152 (66) 1966 f Radiotherapy. Lea & Febiger. Philadelphia, 1960 Amer J 114: 1972 – 2 year suvival : 1983, 4 year NED survival

	No.		s	Survival (%)	)
Series	Patients	Treatment	<2 cm	2-4 cm	>4cm
Bracken <sup>(1)</sup>	68	Surgery/XRT	60	46	13
Grigsby <sup>(2)</sup>	44	Surgery/XRT	89	36	19
Milosevic <sup>(3)</sup>	34	XRT Alone	78	75	12

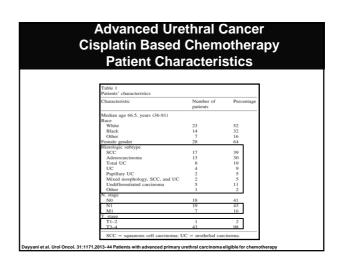
influen	ce or i	umor Site	& Stage	(')
		Percent Survi	val @ 5 Years	
	No. Pts.	Disease Specific	Local Rec Free	Met Free
Site				
Anterior	25	69	53	71
Posterior	13	46	42	48
Entire	27	18	32	24
Stage				
Low <sup>(2)</sup>	12	89	83	88
High <sup>(3)</sup>	49	33	33	36



#### **Female Urethral Carcinoma Radiotherapy: Advanced Tumors** No. 5-Year Survival **Patients** No. Series (%) Delclos et al(1) 25 (28) Weghaupt et al(2) 20 10 (50) Grabstald et al(3) 19 (5) Antoniades(4) 11 4 (36)Hahn et al(6) 8 3 (38)Chu<sup>(7)</sup> 8 0 (0) 29 Total 98 (30)Textbook of Radiotherapy. Lea & Febiger, Phil: Gynecol Oncol 17: 1984 JAMA 197: 1966

Series	No. Patients	No. Alive (%)	Follow-Up Period
Grabstald (1)	20	5 (25)	5 years
Ali et al (2)	5	1 (20)	54 months
Johnson <sup>(3)</sup> & O' Connell	7	3 (43)	1, 1, 12 mos.
Herr (4)	39	21 (54)	5 years

		erapy: Adv		1
Series	No. Patients	Tumor Stage	# Alive NED (%)	Survival Mos. (Range)
Concurrent Che Radiation <sup>(1-</sup>		T2-T3, Nx-N2	4/7 (57)	60 (10-98)
Chemotherapy & Surgery <sup>(3)</sup>	6	C-D2	5/6 (83)	79 (16-156)
Concurrent che /Radiation & Surgery <sup>(1, 4)</sup>	mo 7	T3-T4, N0-N2	5/7 (71)	30 (7-48)



### Advanced Urethral Cancer Cisplatin Based Chemotherapy

- · Based on histologic subtype
  - Squamous cell carcinoma
    - Cisplatin, Gemitabine, Ifosfamide (CGI, 85%)
    - Paclitaxel, Ifosfamide,, Cisplatin (TIP, 15%)
  - Adenocarcinoma
    - Gemcitabine, 5 Fluoroucil, Leucovorin, Cisplatin (GEM-FLP)
  - Urothelial carcinoma
    - Methotrexate, Vinblastine, Doxorubicin, Cisplatin (MVAC), CGI or TIP

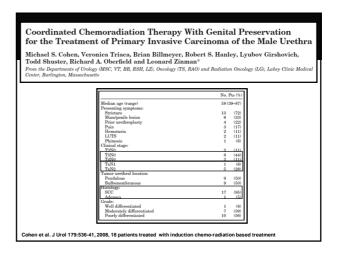
Dayyani et al. Urol Oncol. 31:1171,2013

# | Table 2 | Reposes rates to platinum-containing chemotherapy regimess\* | Regimen | Complete | Partial response | no. (%) | no

# Advanced Urethral Cancer Cisplatin Based Induction Chemotherapy and Surgery

- Total patients
  - -N = 20
- Median survival = 26 mos (2.3-55.7)
- 10/20 (50%) alive median 42 mos
- Local recurrence
  - -N = 3 (15%)
- · Lymph node metastases
  - -N=4/9 (44%) disease free > 3 years

Dayyani et al. Urol Oncol. 31:1171,2013



## Male Advanced Urethral Cancer Chemoradiation: Treatment

- XRT
  - 45-55 Gy in 25 fractions over 5 weeks
  - Inguinal, pelvic nodes, and primary tumor
  - 12-15 Gy boost to primary
- Chemotherapy
  - Concurrent with XRT
    - 5 Fluorouracil
      - IV Infusion D1-4, 29-32
    - Mitomycin
      - IV bolus D1 and 29

Cohen et al. J Urol 179:536-41, 2008

## Male Advanced Urethral Cancer Chemoradiation: Longterm Follow-up

- Patients
  - -N=26
- Median Follow-up
  - 35.5 mos (4-264)
- Complete Clinical Response
  - **19 (79%)** 
    - 42%, disease recurrence, median 12.5 mos
- No Response
  - 5 (21%), DOD

Kent et al. J Urol 193:532, 2015

# **Male Advanced Urethral Cancer Chemoradiation: Longterm Follow-up** 5 year DSS -68% 5 year DFS =43%

Impact of perioperative chemotherapy on survival in patients with advanced primary urethral cancer: results of the international collaboration on primary urethral carcinoma

### Clinical ≥ cT3 or N+ primary urethral cancer (N=26)

- Neoadjuvant Chemotherapy(NAC) or Chemoradiation(N-CRT) (8)
   Surgery ± adjuvant chemotherapy(ACH) (18)

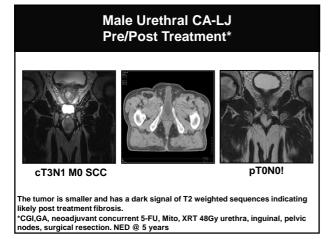
### Overall Survival @ 3 years (p=0.016)

- NAC 100% N=5 N-CRT 100%
- Surgery alone 50%
  N=10
- Surgery+ACH 20% N= 8

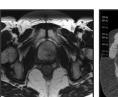
### Predictors of Survival

- Neoadjuvant therapy (p=0.022)
   Posterior tumor location (p=0.005)

15- 10 institutions including 124 patie



### Female Urethral CA-MP Pre/Post Therapy\*







Axial T2. Mass in urethral

Empty diverticulum (yellow) from 2 o clock of urethra

TMP/TA/MVAC, XRT 68 Gy urethra, inguinal, pelvic nodes- NED @ 7 years

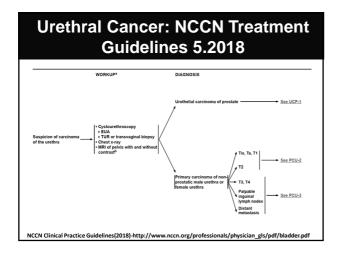
### **Urethral Carcinoma Update 2018:Conclusions**

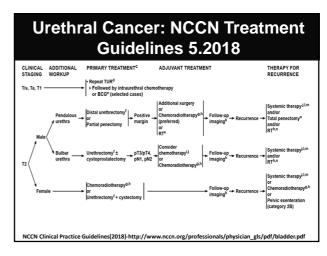
- · Therapy & Prognosis
  - Extent of Disease
    - Size
    - Location
    - T Stage
  - Presence, absence metastasis
    - MRI important!
- · Low Stage, Distal Lesions
  - Male
    - Surgical therapy-Penile Preservation feasible
  - Female
    - Surgery alone
    - Surgery & Radiotherapy

### **Advanced Urethral Cancer Update 2018: Conclusions**

- Multidisciplinary approach is critical
  - Loco-regional control paramount!
  - Distant metastases uncommon @ presentation
- Chemotherapy, radiation and surgery play important roles

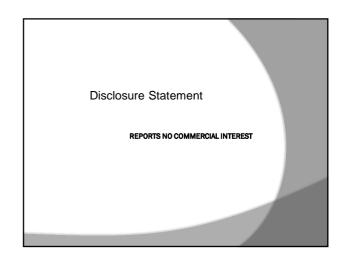
  - Optimal induction chemotherapy regimen has yet to be defined
     Adenocarcinoma, squamous, urothelial histologies respond to cisplatin based agents
    - Adjunct to radiotherapy (neoadjuvant, concurrent)
  - > Surgical resection with negative margins
    - Post chemotherapy or XRT associated with highest rates of local control and survival
    - Morbid
  - > Concurrent Chemoradiation
    - Activity in squamous histology · Evolving role in achieving local control with organ preservation
- Multi-Institutional clinical Trials Imperative!





## DISORDERS OF THE SCROTUM AND SEMINAL VESICLES

MEDICAL COLLEGE OF WISCONSIN Jay Sandlow, MD Professor and Vice-Chair Department of Urology Medical College of Wisconsin Milwaukee, WI



### **Objectives**

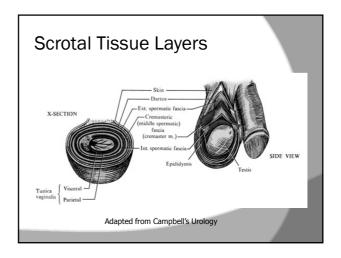
- Review common scrotal disorders and the surgical treatment for them
- Understand the indications for scrotal surgery, as well as the complications
- Understand embryology and anatomy of the seminal vesicles (SV) and how this impacts clinical picture
- Review indications and techniques for SV surgery

### **Outline for Scrotal Topics**

- Anatomy
- Common diagnoses
  - Vasectomy
  - Hydrocele
  - Spermatocele
  - Orchalgia
- Surgery
- Outcomes/Complications

### Anatomy of the scrotum

- Tissue layers
  - Scrotal skin
  - Dartos-continuous with Colles, Scarpa, and the dartos fascia of the penis
  - Tunica vaginalis
- These layers form anatomic barriers to the spread of infection, particularly necrotizing fasciitis
- The testes and epididymides tend to be spared from necrotizing fasciitis of the scrotum



### Anatomy of the Scrotum

- Important to understand blood supply of the scrotal contents
- Testis
  - Testicular (internal spermatic) artery (main blood supply)
  - · Deferential artery from internal iliac -superior
  - Cremasteric (external spermatic) artery from inferior epigastric artery
- Epididymis
  - · Superior epididymal artery derived from testicular artery
- Inferior epididymal artery derived from deferential artery
- Vas deferens
  - · Seminal vesicle end: deferential artery
  - Testicular end: deferential artery and inferior epididymal artery

### **General Preop Principles**

- Scrotum fairly resilient, heals well in the absence of infection, chronic irritation
- Typically, preop antibiotics not required unless pt at risk (DM, advanced age, poor nutrition, etc)
- Recommended antibiotic 1<sup>st</sup> gen cephalosporin or clindamycin (if allergic)
- Clipping/shaving should be done either day of procedure or in the OR

### General Post op Principles

- Compressive dressing prevents swelling, minor bleeding
- Will not prevent hematoma from inadequate hemostasis
- Post op antibiotics not typically necessary unless grossly infected tissue present
- To drain or not to drain, that is the question..

### **Common Scrotal Conditions**

- Vasectomy
- Hydrocele
- Spermatocele
- Chronic orchalgia

### Vasectomy

- Recent AUA Guidelines updated recommendations
- Pre-procedural counseling recommended
- Minimally invasive technique should be used to isolate the vas
- Vasal occlusion with cautery and fascial interposition are recommended
  - Optional techniques acceptable if personal failure rates are low
- Pathology specimen NOT recommended

### Counseling

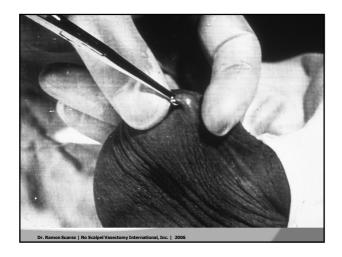
- At a minimum, there should be some type of pre-vasectomy evaluation
- This can be performed in person (preferably), electronically, or over the phone; scheduling pts without any type of evaluation is not recommended.
- Ideally, the pt would also be examined prior to procedure to identify any confounding factors

### Pre-vasectomy counseling

- Patients should understand:
  - Intended to be permanent
  - Not immediate
  - Known failure rate (1:2000)
  - Complication rate is low (~1-2%)
  - Do not need to discuss risks of CaP, etc
- Other forms of contraception should also be mentioned (both permanent and temporary) when applicable

### Isolation and Delivery of the Vas

- Isolate the vas
- Grasp only the vas
- Separate vas from surrounding structures, including vasal vessels
- Perform minimally invasive technique (<10 mm) to access vas only</li>
- NSV instruments ideal for this

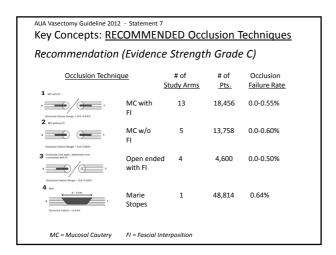


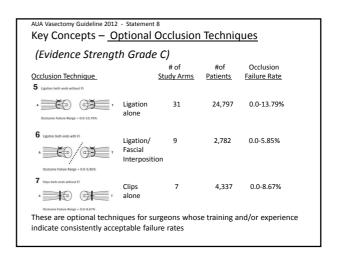




### Procedure

- Occlusion technique
  - Intra-luminal cautery-most effective
  - Fascial interposition-has been shown to reduce recanalization
- Therefore, the evidence shows that mucosal cautery, with or without FI, is the most effective occlusion technique





### Post op recommendations

- Check post vasectomy SA 8-12 weeks (early recanalization can occur within first 6 weeks)
- Patient is considered sterile if there are no sperm or rare, non-motile sperm on a fresh, unspun sample
- If sample is not fresh and sperm are present, motility cannot be commented upon

### Complications

- Rare (~1-2%), include hematoma, infection, chronic testicular pain
- Sperm granuloma may occur, especially if open-ended vasectomy performed
- Not a complication unless symptomatic
- Failure (ie, pregnancy) following confirmation of sterility ~1:2000

### Hydrocele

- Typically a painless swelling of the scrotum
- Represents build up of fluid in the space between the parietal and visceral layers of the tunica vaginalis
- May be caused by lymph overproduction, decreased reabsorption, or a combination
- Often, history of scrotal, inguinal, or lower abdominal surgery, trauma, or inflammation
- Rarely, hydrocele can be presenting sign of malignancy

### Hydrocele

- Ultrasound imaging should be performed to rule out scrotal/testicular masses, as well as to assess whether or not loculations are present
- In adolescents/young adults, communicating hydrocele should be ruled out

### Hydrocelectomy

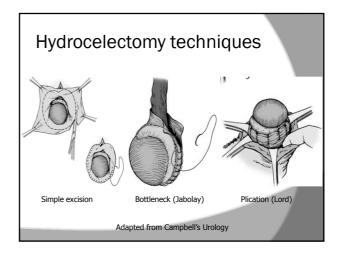
- May use median raphe or transverse unilateral incision
- Care should be taken not to enter the hydrocele sac until it is fully dissected
- Sac is opened under direct vision and fluid is removed
- Sac is then opened completely to expose testis and associated structures

### Hydrocelectomy

- Several methods for repair, including excision, bottleneck (Jaboulay), or plication (Lord)
- Simple excision best for very large, multiloculated, and/or thick-walled sacs
- Typically, 1 cm margin left after excision
- Edges should be oversewn to prevent bleeding

### Hydrocelectomy

- Bottleneck procedure results in less bleeding, but must be sure not to constrict spermatic cord
- Plication best for thin-walled, small or moderate hydroceles.
- Has the lowest blood loss, although if sac is too big, may result in bunching of tissue



### Hydrocele-drain placement

- No good data regarding drain placement after scrotal surgery
- Does not appear to be a difference in complications based on drain
- Some patients may benefit
  - · Complex scrotal surgery
  - · Recurrent hydrocele
  - Excessive fluid production (ascites)
- Penrose for short term (1-2 d), closed system if longer

### Complications of hydrocelectomy

- Typical scrotal surgery complications
  - Bleeding, infection
  - Prevented with meticulous hemostasis
- Recurrence
  - More common with plication, repeat procedures
- Injury to vas deferens/epididymis
  - Up to 10% of cases

### Hydrocele aspiration/sclerosis

- Sclerotherapy best for small hydroceles in men where fertility is no longer desired
- Hydrocele aspirated with 16G angiocath
- 25 cc local anesthesia instilled
- Can use doxycycline, 95% EtOH, or any other sclerosant
- Significant rate of recurrence, may result in multiloculated hydrocele
- Can cause scarring of epididymis

### Spermatocele

- Aneurysmal dilation of tubule within epididymis, typically in caput
- Does not represent an obstruction and only needs treatment if symptomatic
- Distinct from epididymal cyst, which is not connected to epididymal tubule
- Treatment may cause epididymal obstruction
- May recur (or develop anew), so consideration of epididymectomy in men not desired future fertility

### Spermatocelectomy

- Incision similar to hydrocele
- Tunica vaginalis opened following delivery
- Once testis is delivered and exposed, tunica vaginalis over spermatocele is incised
- Spermatocele dissected away from epididymis down to neck entering tubule
- Ligated with small non-reactive suture to prevent further epididymal scarring

### Spermatocelectomy



Adapted from Campbell's Urology

### **Epididymectomy**

- After exposure of testis, dissection typically started at convoluted vas, although if large spermatocele, may start in caput
- Because large spermatoceles may distort anatomy, recommend use of micro Doppler to identify testicular vessels
- Epididymal attachments to testis can be individually ligated/cauterized
- Dissection carried as distally as can be easily accomplished

### **Epididymectomy**



### Complications

- Similar to hydrocele
- Higher risk of recurrence with spermatocelectomy as opposed to epididymectomy
- Damage to vas deferens, epididymis more likely (up to 20%)

### Chronic orchalgia

- Defined as scrotal or testicular pain present for at least 3 months without underlying cause
- If underlying cause determined, should be treated appropriately
- Most patients will have tried NSAID's, antibiotics without improvement or resolution
- Frustrating for patient and provider

### **Evaluation**

- Scrotal ultrasound to rule out underlying pathology (low yield)
- Evaluation for other sources of pain
  - Stone
  - Spinal issues
  - · Secondary gain
- Trial of medications, including NSAID's, anti-depressants, anti-convulsants
- Minimally invasive procedures, such as spermatic cord block

### Surgical treatment-orchalgia

- Vasectomy reversal-rarely indicated
- Microscopic/robotic denervation
  - Should have responded to cord block
  - Can spare vas deferens if fertility still desired
  - Resolution rates up to 75% in selected patients
- Orchiectomy
  - No good evidence of success
  - Last resort
  - Should be via inguinal/subinguinal approach

### **Key Points of Scrotal Surgery**

- Indications for surgery of the epididymis and hydrocele vary, but men of reproductive age should be approached with caution.
- Preoperative imaging with scrotal ultrasonography is almost always indicated.
- Hematoma is the most common complication in scrotal surgery, and extra precautions should be taken to avoid this.

### Outline for Seminal Vesicle Topics

- Anatomy
- Conditions seen
  - SV agenesis
  - SV/ejaculatory duct obstruction
  - Hematospermia
  - Malignancy
- Surgery/interventions

### SV embryology

- Bilateral dorsolateral bulbous dilations of the distal mesonephric ducts about 12 weeks of gestation
- Vas deferens and ejaculatory ducts also form from mesonephric ducts, join with developing SVs
- Typically fully formed by 7 months gestation
- No female equivalent

### SV anatomy

- The arterial supply from the vesiculodeferential artery, branching off from the umbilical artery
- Venous drainage follows the arterial supply draining through the vesiculodeferential veins and the inferior vesicle plexus
- Innervation by the hypogastric nerve (adrenergic and cholinergic) and the pelvic nerve
- Lymphatic drainage through the internal iliac nodes

### SV physiology

- Seminal vesicle secretions contribute 50% to 80% of the volume of the ejaculate
- The pH of the fluid is neutral to slightly alkaline
- The fluid contains fructose and other carbohydrates necessary for sperm motility
- It also contains a coagulation factor and prostaglandins A, B, E, and F

### SV conditions

- SV agenesis
- SV/ejaculatory duct (ED) obstruction
- Hematospermia
- Malignancy

### SV agenesis

- Bilateral associated with CBAVD, CF
- Unilateral often associated with ipsilateral renal agenesis/anomaly
- Important to identify associated disorders

### Bilateral SV agenesis

- Typically associated with CBAVD
- Patient usually present with infertility
- Most often due to mutation of CFTR and/or 5T allele
- Genital form of CF, requires genetic counseling
- Actual involution of vasa, SV during fetal development
- No surgical treatment possible

### Unilateral SV agenesis

- Not uncommon, incidence 0.6-1.0%
- May be diagnosed during evaluation for infertility or in case of unilateral vasal agenesis
- Often associated with ipsilateral renal agenesis
- Defect due to mesonephric duct problem early (6-8<sup>th</sup> week of gestation), leading to agenesis of genital ducts and ipsilateral kidney
- Thus, if patient negative for CFTR/5T mutation, renal U/S indicated
- Although not surgically correctable, important to know

### Surgery of the SV

- Several operative approaches have been described
- These include transvesical, transcoccygeal, transperineal, paravesical, and retrovesical
- These are for historical interest only, as nearly all "open" surgery on the SV are now done utilizing minimally invasive techniques
- Endoscopic and transrectal procedures continue to be the most common

### SV/ejaculatory duct obstruction

- May be due to trauma, infection, cysts
- Can be total or partial, although partial difficult to assess
- TRUS best test for diagnosis
- MRI reserved for equivocal cases, suspected solid lesions
- Treatment typically only necessary if suspicious for malignancy, symptomatic or infertility present

### TRUS-guided aspiration

- Used for drainage of symptomatic SV cysts
- Can be sclerosed if recurrent
- Can also be treated endoscopically using TUR or Collins knife (if close to prostate)

### TUR-ED

- Indications very specific, include infertility and ejaculatory pain (rare)
- Risks and side effects significant, must be outweighed by potential benefit
- In patients with non-azoospermic infertility (ie, partial EDO), consider sperm banking

### Surgery of the SV





Adapted from Campbell's Urology

### TUR-ED

- Resectoscope with small loop used
- Try to minimize cautery, use pure cutting
- Goal is to unroof cyst or obstruction, not remove prostate
- Typically leave catheter until urine is

### Hematospermia

- Typically benign condition
- May be due to inflammation with/without infection, trauma, mass
- Usually self-limiting, may be persistent
- If persistent, TRUS recommended to assess SV, ED, prostate
- Treatment typically NSAID's, supportive care

### SV masses

- Cysts
- Benign tumors
  - Cystadenoma
  - Amyloid
- Malignant tumors
  - Adenocarcinoma
  - Sarcoma
  - metastatic

### Malignancy

- Most malignancies of SV are metastatic; primary SV tumors are rare
- Often present late in clinical course
- Imaging should start with TRUS (with biopsy), endorectal MRI
- Minimally invasive techniques best option for treatment

### Key Points for SV Surgery

- Seminal vesicle secretions contribute 50% to 80% of the volume of the ejaculate.
- Normal seminal vesicles are not palpable on digital rectal examination.
- Unilateral seminal vesicle agenesis may be associated with ipsilateral renal anomalies and unilateral absence of the vas deferens.
- If there is a palpable seminal vesicle abnormality, TRUS should be performed with biopsy if there is suspicion for malignancy.
- Benign and malignant tumors of the seminal vesicles are very rare.

### Conclusions

- Scrotal disorders one of the most common conditions seen in urology
- Various presentations, ultrasound mainstay for diagnosis
- Meticulous surgical technique will prevent most complications
- Most SV disorders benign, can be diagnosed with TRUS
- Occasional need for MRI, other imaging modalities

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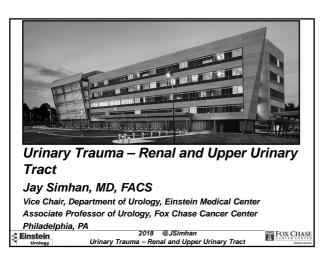
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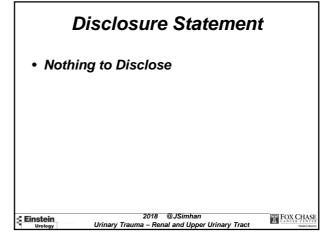
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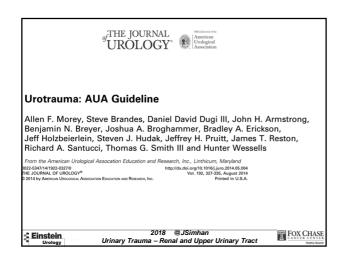
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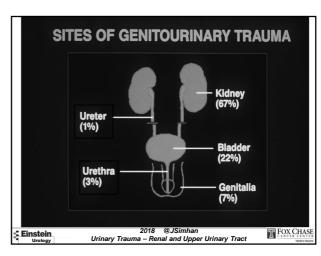
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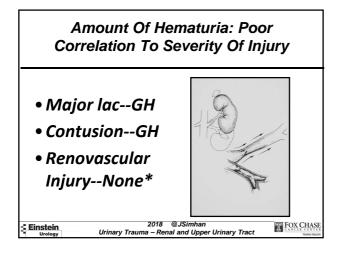
  Figures reprinted from Campbell-Walsh Urology, 9th edition, Sandlow JI, Winfield HN, Goldstein M. Surgery of Scrotum and Seminal Vesicles, Ch. 34, Copyright 2007, with permission from Elsevier.

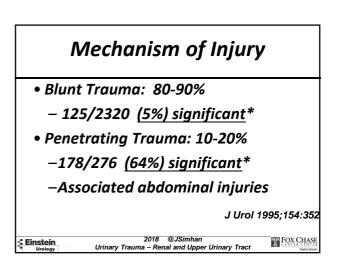


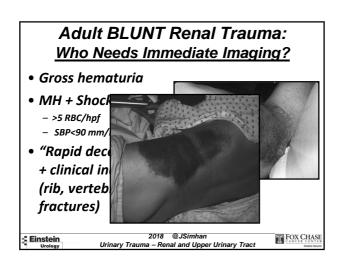












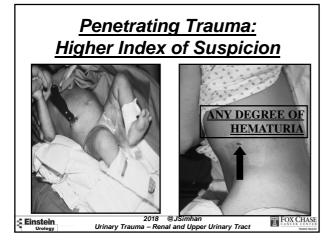
# Blunt Trauma: When Can Imaging Safely Be Spared?

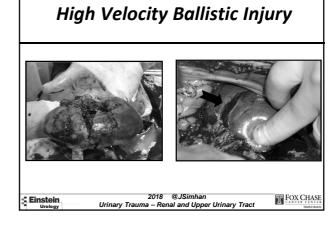
- Isolated microhematuria
  - No shock, symptoms, signs of multisystem trauma
- \*\*Peds: < 50 RBC/hpf\*\*</li>
  - -SFGH 25-year experience (n=374)

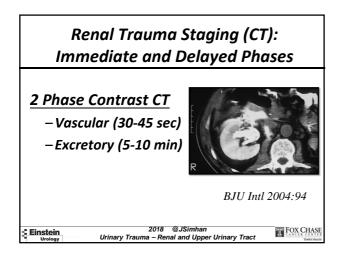
Buckley et al, J Urol 2004:172

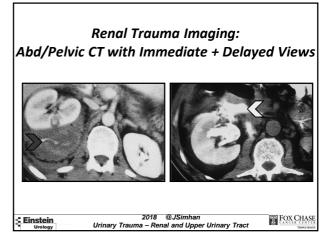
Einstein 2018 @JSimhan

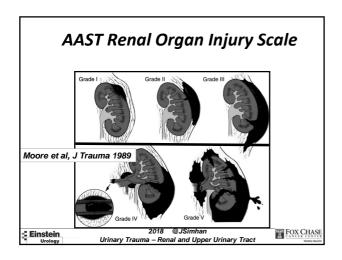
Urinary Trauma – Renal and Upper Urinary Tract

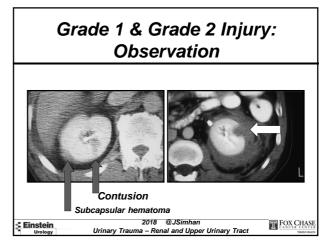


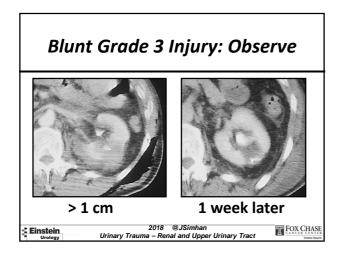


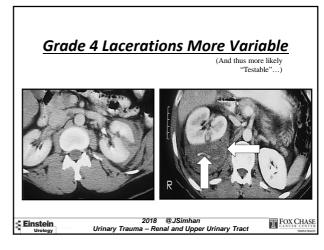


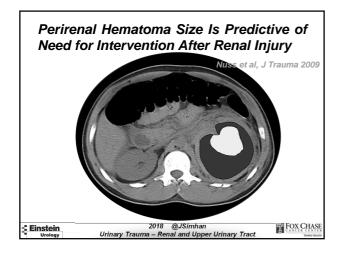


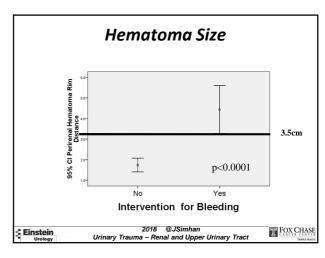


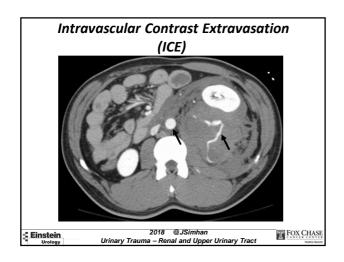


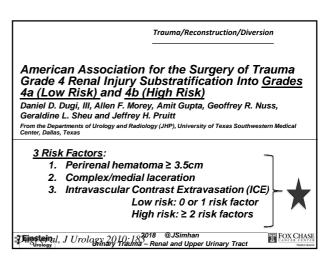




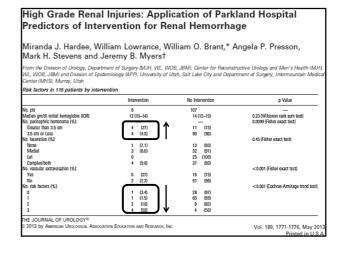


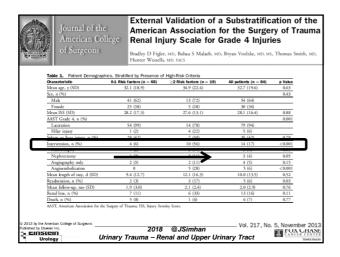


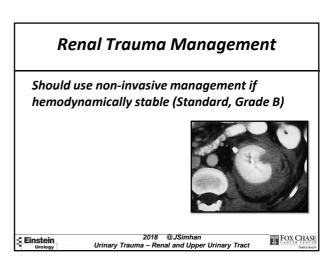




### Low Risk vs High Risk **Low Risk High Risk** (3/4a)(4b)Intervention 6/84 12/18 (+)(7.1%)(66.7%)Odds ratio 1 26.0 p<0.0001 2018 @JSimhan Urinary Trauma – Renal and Upper Urinary Tract TOX CHASE Einstein







### Renal

Must perform immediate intervention (surgery or angioembolization in selected situations) in hemodynamically unstable patients with no or transient response to resuscitation. (Standard; Evidence Strength: Grade B)

Einstein

2018 @JSimhar

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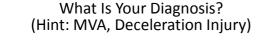
### Damage Control— **Consider Nephrectomy**

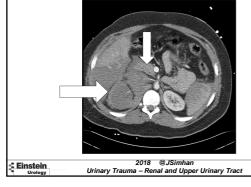


- >3u PRBC transfused?
- Unstable?
- CT: Complex injury? Grade 5?

018 @JSimhan

FOX CHASE





# **Renal Pedicle Avulsion** 2018 @JSimhan a – Renal and Upper Urinary Tract FOX CHASE

### **Renal Vascular Laceration**

- Vein: better prognosis than artery
  - -Left RV may be ligated if proximal (adrenal, gonadal)
- Arterial: usually results in nephrectomy

FOX CHASE Urinary Trauma – Renal and Upper Urinary Tract

### Shattered Kidney (Grade 5): Nephrectomy Unless Completely Stable





Einstein

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### Critical Points for Kidney Trauma

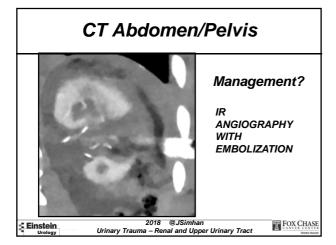
- . Know the AAST Grades dictate treatment
- Stabilize the patient save nephrons when possible!
- · Angiography/Surgery for unstable patients
- Reimage higher grade injuries after 48-72 hrs

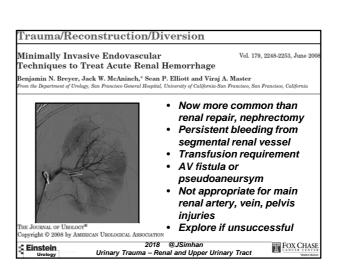
Finetoin	2018 @JSimhan	T FOX CHASE
Einstein Urology	Urinary Trauma – Renal and Upper Urinary Tract	TEMPLE HEALTH

### Case

- 22M sustained trans-abdominal GSW. Unstable
- Taken to OR emergently for control of bleeding
- R Nephrectomy performed. Pt stabilized in ICU
- CT A/P obtained

	Einstein	2018 @JSimhan Urinary Trauma – Renal and Upper Urinary Tract	FOX CHASE
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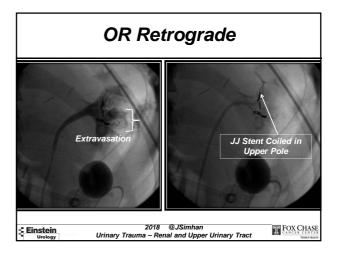


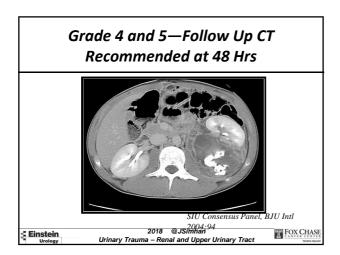
- Patient was stabilized after IR embolization
- 2 days after embolization, pt becomes anuric, JP drain starts draining over 2-3 liters/day, Next Step:
- A. Observation
- B. Repeat CT Scan
- C. Angiography
- D. OR for Nephrectomy
- E. Retrograde Pyelogram

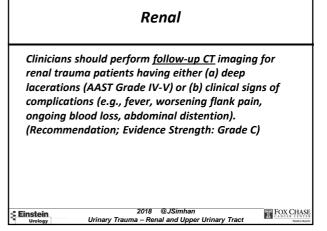
Einstein
Urinary Trauma – Renal and Upper Urinary Tract

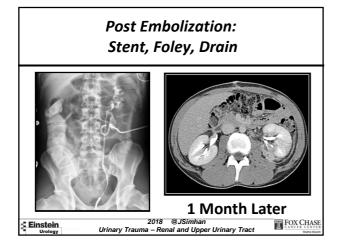
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Urinary Trauma – Renal and Upper Urinary Tract





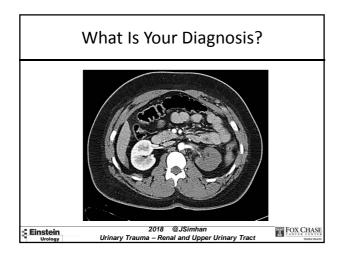


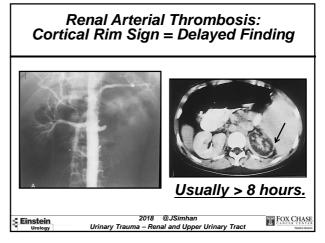


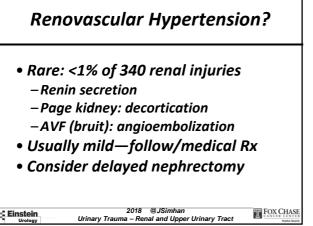


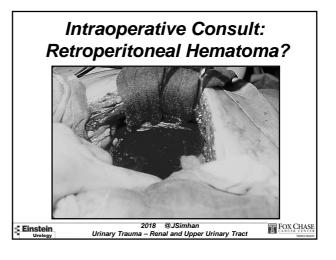


# • Clinicians should perform urinary drainage in the presence of complications such as enlarging urinoma, fever, increasing pain, ileus, fistula or infection. (Recommendation; Evidence Strength: Grade C) • Drainage should be achieved via ureteral stent and may be augmented by percutaneous urinoma drain, percutaneous nephrostomy or both. (Expert Opinion)







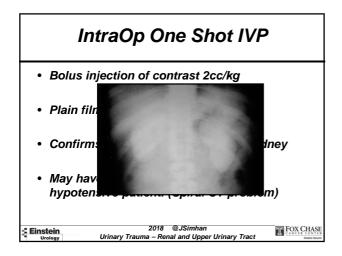


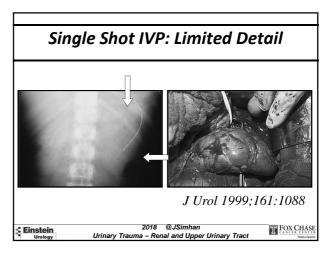
### Absolute Relative Hemodynamic • Non-viable tissue instability • Persistent Urinary Expanding extravasation pulsatile · Renal artery hematoma · Surgery for • Major injury associated injury solitary kidney 2018 @JSimhan Urinary Trauma – Renal and Upper Urinary Tract

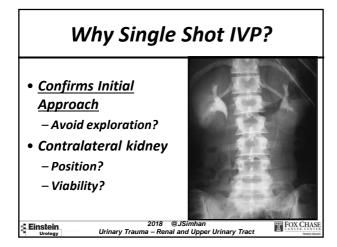
Indications for Renal Exploration

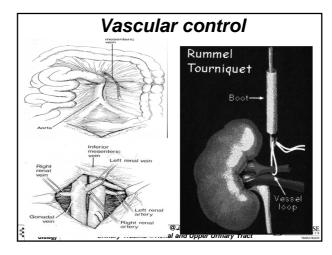
## IntraOp One Shot IVP · Bolus injection of contrast 2cc/kg • Plain film after 10 minutes • Confirms presence of contralateral kidney · May have to wait longer longer for hypotensive patient. (Spiral CT problem) 2018 @JSimhan Urinary Trauma – Renal and Upper Urinary Tract T FOX CHASE Einstein

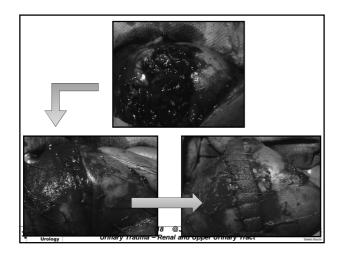
T FOX CHASE



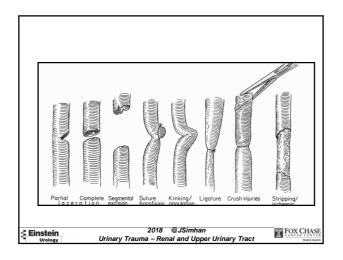








# Principles of Renal Reconstruction Midline incision Early vascular control Total renal exposure Debridement/hemostasis Water-tight closure/ cover defect Penrose drain (not suction)



# Ureteral Trauma: Indicators? High Index Of Suspicion

- Hypotension 50%
- Hematuria absent in 25%
- Dx made by 1 shot IVP 7/19 (36%)
- No single test reliably excludes dx

J Urol 2003:170;1213

Einstein 2018 @JSimhan
Uroleay Urinary Trauma – Renal and Upper Urinary Tract

### Ureteral Trauma: 10 Yr LA County Experience

- Penetrating trauma 95%
- Associated injuries 97%
- Preoperative imaging 12%
- Intraoperative diagnosis 77%

J Urol 2005;173:1202

Einstein
Urinary Trauma – Renal and Upper Urinary Tract

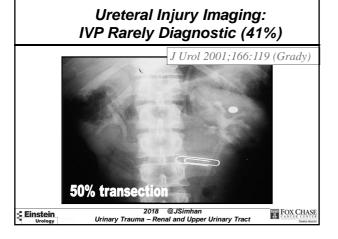
Urinary Trauma

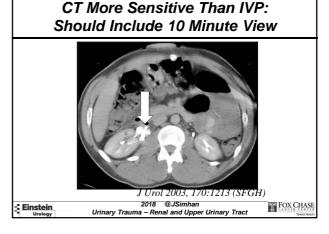
### **Ureteral Trauma Imaging**

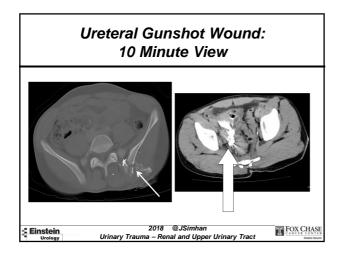
Clinicians should perform IV contrast enhanced abdominal/pelvic CT with delayed imaging (urogram) for stable trauma patients with suspected ureteral injuries. (Recommendation; Evidence Strength: Grade C)

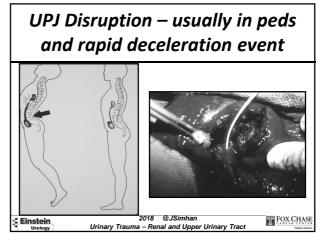
Einstein
Urology Urinary Trauma – Renal and Upper Urinary Tract

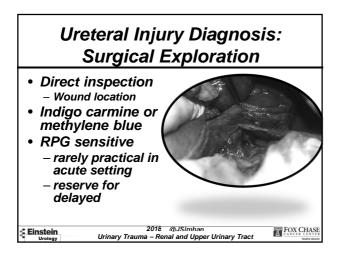
Urology Urinary Trauma – Renal and Upper Urinary Tract

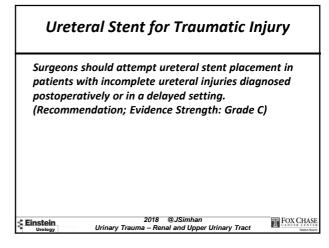


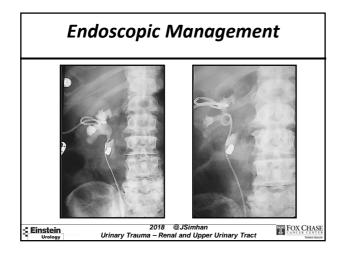


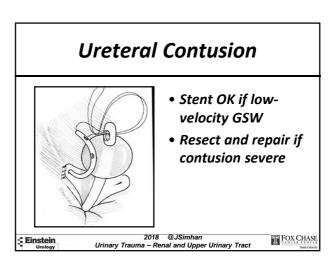












### **Iatrogenic Ureteral Injuries**

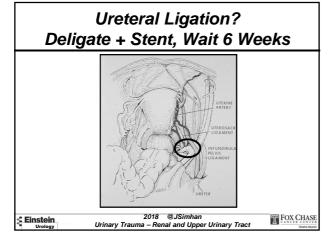
- Leading cause (~80%)
- Gyn > 50% (TAH): distal 1/3
  - GU, Vasc, Colorectal, Gen Surg
  - Ureteroscopic injuries now uncommon
- Prior XRT, intraop bleeding, fibrosis, RP mass increase risk
- Stent does not assure prevention, may assist in intraop recognition

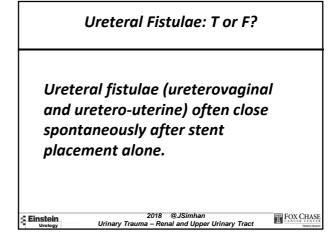
FOX CHASE Einstein Urinary Trauma – Renal and Upper Urinary Tract

### Timing of Ureteral Repair: When Is Injury Recognized?

- Intraoperative
  - Immediate repair preferred
- < 5 days & stable
  - Retrograde pyelogram + Stent preferred
  - Immediate repair OK if complex
- 5 or more days—complications more likely
  - Stent or nephrostomy
  - Drain urinoma
  - Delayed reconstruction

2018 @JSimhan T FOX CHASE Einstein Urinary Trauma – Renal and Upper Urinary Tract





### Ureteral Fistulae: **True**

Ureteral fistula (ureterovaginal and uretero-uterine) often close spontaneously after stent placement alone.

(now in the newly updated AUA Guidelines as well)

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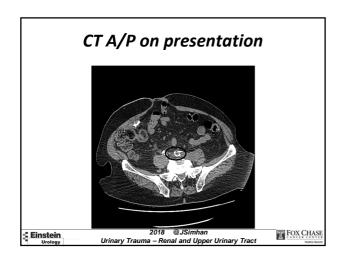
Br J Urol 1993:65:453

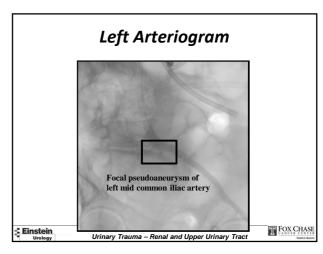
FOX CHASI

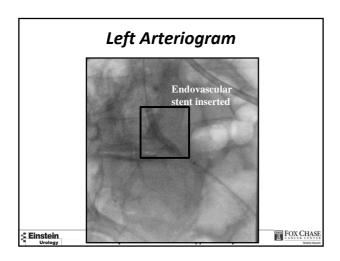
### 71M--Gross Hematuria

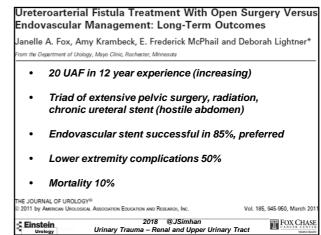
- Metastatic CaP s/p XRT with subsequent radiation cystitis
- Cystectomy with ileal conduit Jan 2013
- On ADT currently managed with Sipuleucel T (Provenge)
- Known Left uretero-enteric stricture currently managed with indwelling metal ureteral stent (last exchanged early 09/2013)
- Transferred from OSH with gross hematuria from conduit

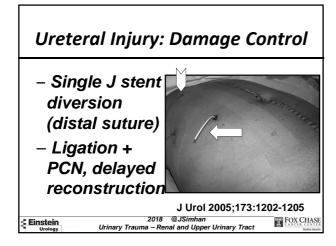
2018 @JSimhan Urinary Trauma – Renal and Upper Urinary Tract FOX CHASE

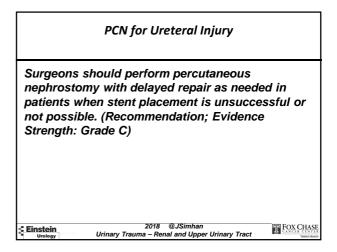








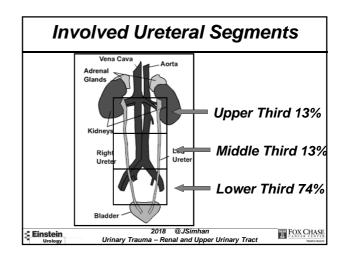


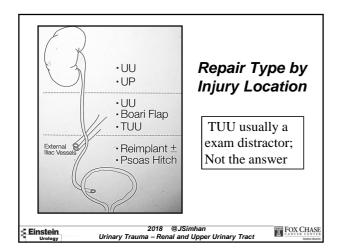


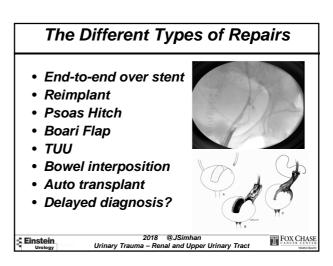
FOX CHASE

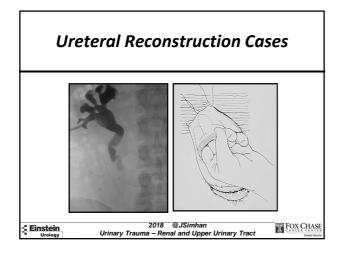
# Principles of Ureteral Repair Debride non-viable tissue Wide spatulation Tension-free Watertight closure Stent Peri-ureteral drainage (+/-)

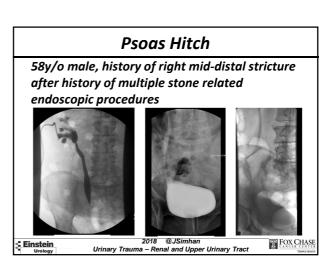
Einstein

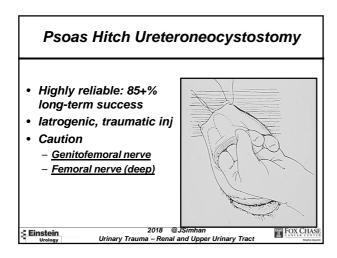












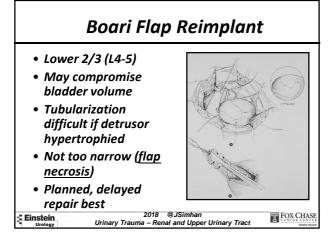
### **Pearls of Psoas Hitch Reimplant**

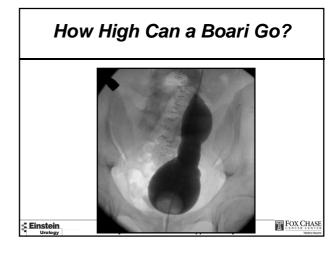
- Mobilize contralateral superior bladder
- Hitch bladder <u>prior to reimplantation</u>-straight ureteral tunnel with 2 to 4 sutures (absorbable)
- Refluxing, spatulated anastomosis, stent

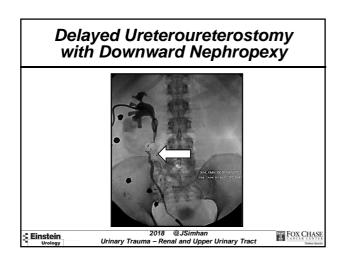
Marshall, J Urol 1997;158:2078

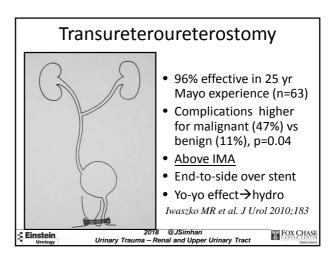
Einstein 2018 @JSimhan
Urinary Trauma – Renal and Upper Urinary Tract

Urology Urinary Trauma – Renal and Upper Urinary Tract

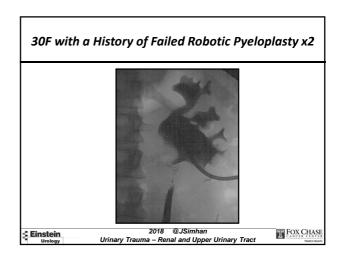


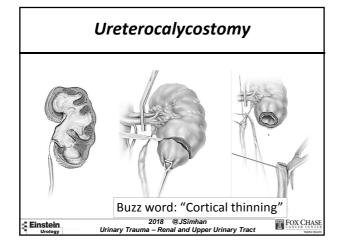


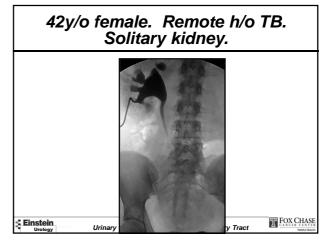


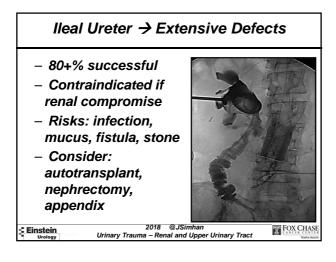


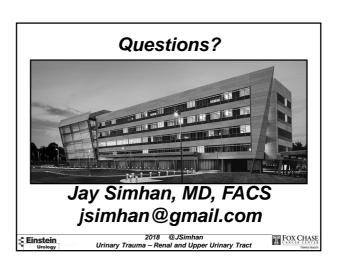
### **Transureterosureterostomy Indications**: Contraindications: · Planned, Delayed · Pelvic radiation · Bladder small, Reflux fibrotic, pelvic abscess • Stone disease • Extensive lower · Cancer, TB, RPF ureteral defect 2018 @JSimhan Urinary Trauma – Renal and Upper Urinary Tract FOX CHASE Einstein

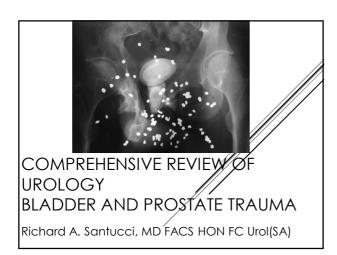












► Nothing to Disclose

DISCLOSURE STATEMENT

Bladder: Grade • AAST Organ Injury Severity Scale Contusion or intramural hematoma Hematoma Laceration Partial thickness laceration Laceration Extraperitoneal, less than 2 cm Laceration Extraperitoneal, greater than 2 cm Intraperitoneal, less than 2 cm Intraperitoneal greater than 2 cm IV Laceration Laceration Intraperitoneal or extraperitoneal, extending to 3 bladder neck or ureteral orifice

Bladder: BLUNT: Overview

Rare: <2% of all injuries requiring surgery

Often with a severe associated injuries

Often high-energy injuries

Associated with urethral rupture 10-29% and pelvic fracture 6-10%

Bladder: PENETRATING: Overview

- Civilian incidence 2%
- Associated major abdominal injuries (35%) and shock (22%)
- Mortality high: 12%

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Bladder: Diagnosis: Physical Signs

- Suspicion: required in cases of penetrating trauma (no time for studies): trajectory.
- Physical signs:
  - Abdominal pain
  - Abdominal tenderness
  - Abdominal bruising
  - Urethral catheter does not return urine
  - Delayed?
    - Fever
    - No voiding
    - Peritoneal signs
    - TBUN

6

### Bladder: Diagnosis: Hematuria

- Most (95%) have gross hematuria
- Microhematuria does occur: usually with minimal injury

7

Bladder: Diagnosis: Plain Cystography



- Nearly 100% accurate when done properly:
  - Adequate filling with 350 cc or stop with pain
  - Drainage films
- Use 30% contrast
- Underfilling (250 cc)/ associated with false 8 negatives

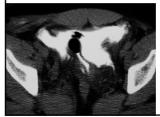
### Bladder: Diagnosis: CT Cystography

- Preferred, especially if already getting other CTs
- Anterograde filling by "clamping the Foley" is not OK!
- Must dilute contrast (6:1 with saline, or to about 2-4%)
- Expect 1 in 10 to be positive

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Extraperitoneal

Intraperitoneal





### Bladder: Extraperitoneal Rupture

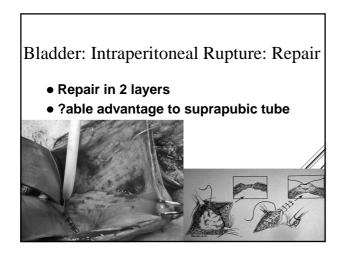
- Alone in 62% of cases
- Combination with intraperitoneal 12%
- Treat "nonoperatively" but watch out for 26% complication rate.
  - Bone fragment in bladder
  - Open pelvic fracture
  - Rectal perforation
  - Poor drainage secondary to bleeding/clots
  - Undergoing laparotomy anyway
  - Undergoing pelvic ORIF anyway
  - 11 - Fewer complications (early 5 vs 12%, late ∕5 vs 21%)

### Bladder: Extraperitoneal Rupture: Repair



- Open bladder and inspect from the inside out
- Check for associated urethral, bladder neck, prostate and rectal injuries
- Repair in 1 layer from the inside
- +/- suprapubic tube//

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### Bladder Rupture: Complications

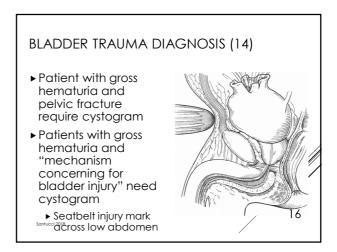
- Foley can be removed in 85% by 10 days
- Generally rare complications
- Acute, self limited urinary frequency is common (gone by 2 months)
- Persistent urinary frequency in 2%

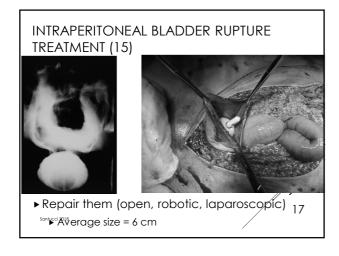
antucci 2018

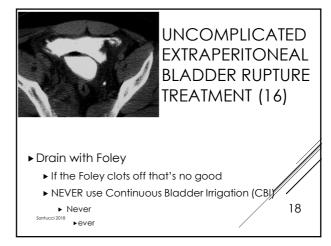
14

▶Review of what the AUA guidelines say on the subject

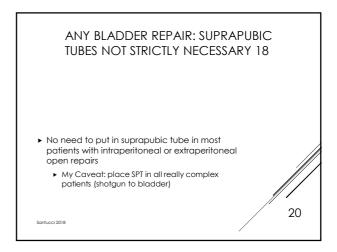
Santucci 2018

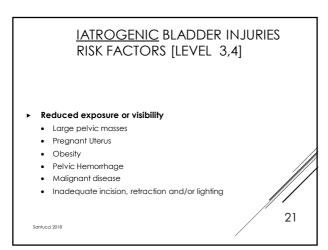






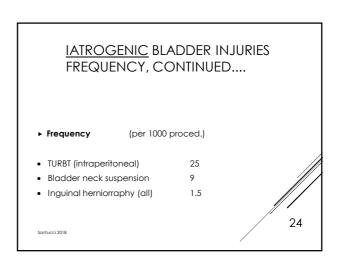
# COMPLICATED EXTRAPERITONEAL BLADDER RUPTURE 17 • Do laparotomy, repair • Definition • Pelvic fracture shards in bladder (these never heal) • Concurrent rectal or vaginal lacerations (head off fistula) • Bladder neck injuries especially in children (not to save continence: to decrease risk of severe sepsis) • Having ORIF pelvis by ortho anyway (keeping urine off their hardware) • Having laparotomy anyway sontuce(after they fistulize to laparotomy wound)





# IATROGENIC BLADDER INJURIES RISK FACTORS [LEVEL 3,4] • Anatomy Distortion • Adhesions/previous pelvic surgery • Pelvic organ prolapse • Congenital anomalies • Radiation therapy • Chronic inflammatory pelvic disease • Endometriosis • Malignant infiltration • Distended/thin bladder

<u>IATROGENIC</u> BLADDER INJURIES				
Most frequently injured organ during pelvic surgery				
[level of evidence 3]				
► Frequency (per	1000 proced.)			
<ul> <li>Vaginal Delivery</li> </ul>	0.1			
<ul> <li>C Section</li> </ul>	1.8			
<ul> <li>Gynecological Surgery (open)</li> </ul>	1.5			
<ul> <li>Vaginal Hysterectomy</li> </ul>	9			
<ul> <li>Radical Cancer Hysterectomy</li> </ul>	14			
<ul> <li>Obstetric Hysterectomy</li> </ul>	61 ///			
<ul> <li>Gynecological Surgery (Lapare</li> </ul>	oscopic) 3 ///			
<ul> <li>Lap. Assist. Vaginal Hyst.</li> </ul>	28 <sub>23</sub>			
Santucci 2018	/ 25			



### **IATROGENIC BLADDER INJURIES**

- ► Should be identified and repaired immediately
- ► Constant surgeon's suspicion and awareness is crucial
- Laparoscopic surgery entails a risk 2 to 10-fold larger than standard open procedures

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## IATROGENIC BLADDER INJURIES ACUTE PRESENTATION

- \* Clear fluid in the operative field
- \* Visible bladder laceration
- \* Gas distension of the urine bag (laparoscopy)

### Confirmatory procedures in the OR

- Direct inspection of the bladder walls
- Intravesical instillation of diluted Methylene blug irrigation fluid through Foley catheter
- Cystoscopy
- **entuccidantentional cystotomy to inspect!**

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## IATROGENIC BLADDER INJURIES ACUTE PRESENTATION

### ► PRINCIPLES OF REPAIR

- \* Same as bladder injuries from external trauma
- \* Injuries at laparoscopy can be repaired laparoscopically if: [level of evidence 4,5)

Small injury

Adequate expertise

Adequate view and exposure

Ureters or bladder neck not compromised

Santucci 2018

IATROGENIC BLADDER INJURIES DELAYED PRESENTATION

- \* Hematuria
- \* Oliguria
- \* Elevation of BUN/Creatinine ratio
- \* Lower abdominal pain and distension
- \* Peritonitis/Sepsis
- \* Fistula

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### **BLADDER QUESTIONS**

A 43-year old woman sustains a single gunshot wound to the abdomen. You are consulted at the time of emergency laparotomy for an obvious bullet hole in the dome of the bladder. You should:

- a. open the bladder anteriorly and inspect the inside of the bladder
- b. perform an intraoperative cystogram
- c. debride the bullet hole and close it in two layers
- d. perform an intraoperative IVP
- e. place a ureteral stent

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### **BLADDER QUESTIONS**

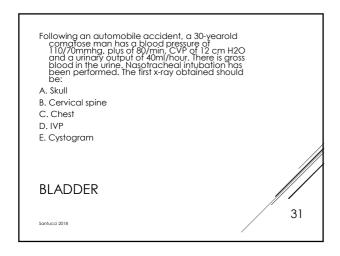
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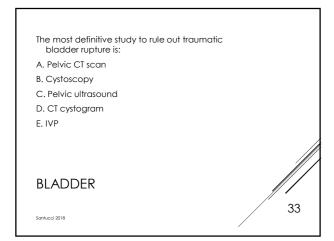
A: Inspect that bladder! (note that a bullet that made one hole in dome is likely to make a second hole elsewhere as it passes through)

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Following an automobile accident, a 30-yearold complose man has a 80 pp. 20 pp.



The most definitive study to rule out traumatic bladder rupture is:

A. Pelvic CT scan

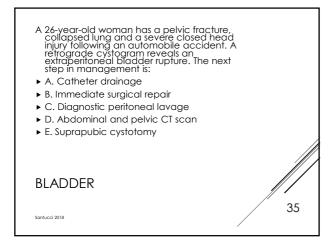
B. Cystoscopy
C. Pelvic ultrasound

D. CT cystogram
E. IVP

D: CT cystogram (or plain cystogram but not offered)

BLADDER

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A 26-year-old woman has a pelvic fracture, collapsed lung and a severe closed head injury following an automobile accident. A retrograde cystogram reveals an extraberitioneal bladder rupture. The next step in management is:

• A. Catheter drainage

• B. Immediate surgical repair

• C. Diagnostic peritoneal lavage

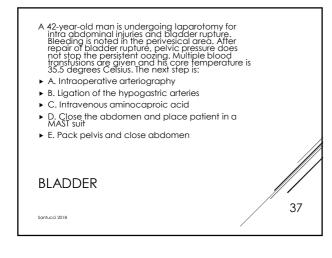
• D. Abdominal and pelvic CT scan

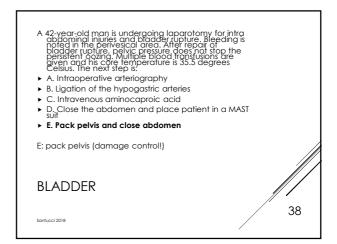
• E. Suprapubic cystotomy

A: catheter drainage

BLADDER

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#### **Urethral Trauma**

Thomas G Smith III, MD FACS Baylor College of Medicine Houston, TX USA

#### Disclosures

- Industry or pharmaceutical support: None
- Male urethral injury management: None

#### Objectives

- Review epidemiology, etiology, evaluation, management, and complications of urethral trauma
- Classification

  - Traumatic
    Evaluation
    Management
    Iatrogenic
    Management
    Management
    Management

  - Impact
     Artificial Urinary Sphincter (AUS) Erosion
  - IncidenceManagement

#### Introduction – Urethral Trauma

- The urethra is not commonly injured from external violence and only accounts for 4% of all genitourinary trauma
  - Majority of urethral injuries are the result of blunt force trauma
- Anatomic categorization of injury: urethra divided into the anterior and posterior segments at the level of the genitourinary diaphragm
- Due to anatomic position, each segment has very different sources of injury and initial treatment options
- Most urethral injuries occur in men due to the longer urethral length and higher incidence of traumatic injuries in men

#### **Definitions**

- - Refers to injury caused by external force from a variety of mechanisms, including traffic- or transportation-related injuries, falls, assault (e.g., blunt weapon, stabbing, gunshot), explosions, etc.
- Injuries
  - Are the results of trauma and the force imparted on the particular body part of organ.
  - Typically categorized as blunt or penetrating based on mechanism
  - Blast injuries are unique and have components of both blunt and penetrating mechanism

#### Definition - Urethral Trauma

- Urethral injuries are dependent on the anatomic location (anterior versus posterior)
- The impact, complications, and management of urethral injuries are highly variable and greatly dependent on the mechanism, involvement of surrounding structures, and severity
  - . Blunt injuries: Contusion, laceration, and avulsions
  - Penetrating injuries: Laceration, transection, and blast injury with delayed stenosis
  - <u>latrogenic</u>: Result from endoscopic injuries and instrumentation
    - Range from minor mucosal abrasions, to lacerations and penetrations, and thermal injury

#### **Epidemiology**

- Incidence of trauma is rising
- $\bullet$  WHO estimates that by 2020 road traffic injuries will be the  $6^{th}$  leading cause of death
- Renal trauma occurs in 1-5% of all trauma cases (Santucci, Wessells et al. 2004)
  - The kidney is the most commonly injured genitourinary organ
     Incidence of renal injury of 4.89 per 100,000 persons
  - (Wessells Sub et al. 2003)
  - Recent NTDB reports estim
     7% of total injuries nate solid abdominal organ injuries occur in approximately (Hurtuk, Reed et al. 2006)
  - . Based on current US population data 15000 persons will sustain renal injury annually

#### **Epidemiology**

- Pelvic injuries occur in 5% of all injuries in the United States
- Urethral and bladder injuries occur in 10-15% of pelvic fractures
  - (Bariol, Stewart et al. 2005), (Paparel, N'Diaye et al. 2006)
    Recent estimate of the incidence of pelvic fracture injury was greater than 31,000 over a five year period (Bjurlin, Fantus et al. 2009)
  - Based on that current population, > 6000 urethra and bladder injuries occur in the same time period
  - Urethral injuries are often associated with specific fracture patterns
    - . (Basta, Blackmore et al. 2007)

#### Epidemiology - Iatrogenic Urethral Trauma

- Incidence of urethral catheterization
  - No exact incidence or number of inpatients catheterized
    - 24 million catheters are purchased by hospitals each year (Saint et al, 2000)
       Estimates outside the US are 10-25% of hospitalized patients (Jain et al, 1995)
    - One study noted 11000 catheter placements per year (Davis et al, 2016)
- Incidence of urethral injury

  - 0.3-3% of hospitalized patients incur latrogenic injury (8hatt et al 2015)
     0.7-6.7 per 1000 male urethral catheterizations (Kashefi et al 2006, Davis et al 2016)
- Impact on urology consultations

  - 6% of urology consultations (864 total) (Thomas et al, 2009)
     32.9% of urethral injuries over a five year period (Dobrowd)

#### Anatomy – Urethral Trauma

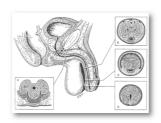
- The male urethra is anatomically divided into two areas referred to as the anterior and posterior urethra
  - The genitourinary diaphragm is the point of anatomic differentiation

  - Components of the anterior urethra distal to proximal
     Fossa navicularis
     Penile or pendulous
     Penile urethra and fossa navicularis comprise slightly more than half of the distal anterior urethra
    - External to the body in the penis
    - Bulbar segments
       Posterior urethra is composed of two segments
       Membranous

      - Prostatic
         Both intimately related to the bony pelvis and are injured more frequently in pelvic fractures

#### Anatomy – Urethral Trauma

• Urethral Anatomy (Gross)



#### Anatomy – Urethral Trauma

- Blood supply to the urethra arises proximally from the internal pudendal
  - Becomes the common penile artery which terminates into the bulbourethral
  - Common penile and bulbourethral arteries are the main blood supply to the
    - These arteries arborize in the glans of the penis and retrograde perfusion of the urethra is maintained when the bulbar arteries are transected.
- Small perforating arteries from the inferior aspect corporal bodies then enter the dorsal urethra at their attachment
- The venous outflow of the urethra parallels the arterial supply

# Anatomy – Urethral Trauma Urethral Blood Supply

# Etiology – Urethral Trauma

#### Etiology - latrogenic Urethral Trauma (AUS)

- Erosion Rates
  - Contemporary series 5-10% (laietal 2007)
  - Recent high risk series reported rate of 6.2% (Brandt et al, 2016)
  - Some discrepancy due to concomitant infections
- Etiology
  - Early erosion due to iatrogenic urethral injury
  - Late erosion due to other iatrogenic factors, e.g. catheter placement
  - Subset of spontaneous erosions

#### Presentation – Urethral Trauma

- Based on the anatomic differences of the male and female urethra urethral injuries have a variable presentation
- Most of these injuries are located in the mid-perineum, where the urethra is crushed against the pubic arch
   Penetrating injuries present with obvious wounds to the perineum or penis.

- Posterior:

  Present in the context of severe multisystem trauma

  The initial steps in evaluation include the ABCs growsy, breathing, and girculation

  Although patients, cannot be directly interviewed, information concerning mechanism of injury, blunt versus should be obtained also of that mechanism, it.e. high speed mortervelice. Coolision or high velocity missile injury, should be obtained also of that mechanism, it.e. high speed mortervelice. Coolision or high velocity missile injury, should be obtained by the coolision of the coolision of
- - Female urethral injuries are associated with 0-6% of patients with pelvic fracture
     Female patients with urethral injury may have hematuria or vaginal lacerations

#### Presentation – Urethral Trauma

- Physical Exam Findings
  The classic triad of blood at the urethral meatus, inability to void, and palpably distended bladder is uncommon in clinical practice
  Blood at the urethral meatus is variable in
  - Blood at the urethral meatus is variable in presentation and occurs in 37-93% of patier
  - Patients who present with blood at the urett meatus, especially in the setting of pelvic trauma, evaluation of the urethra is mandat Patients with bulbar urethral injuries may present with a perineal hematoma

  - Patients with posterior urethral injuries may have a "high-riding" or balottable prostate on exam



#### Presentation – latrogenic Urethral Trauma

- Etiology
  - Inadvertent inflation of balloon in the urethra
     Balloon pressures reach > 700 kPa (≈ 102 PSI)

  - False passage at the level of the bulbar or penile urethra
- Diagnostic Criteria
  - Blood per urethra/Gross hematuria with catheter placement
     Non-draining catheter

  - Penile/Perineal pain
  - Cystoscopic evidence of urethral injury
  - Contrast extravasation on retrograde urethrogram

#### Presentation - latrogenic Urethral Trauma (AUS)

- Symptoms
  - · New onset incontinence
  - Hematuria
  - Urinary tract or genital skin infection
- Evaluation
  - Physical exam
  - Cystoscopy



#### **Urethral Trauma**

- Evaluation Which patients
  - Guideline statement 19
  - Patients with blood at the urethral meatus after pelvic fracture

    - Blood at meatus

      37-93% in posterior urethral injur

      75% in anterior urethral injury

      (Mouraviex, Coburn et al. 2005), (Egammal 2009)

      No attempt at catheter placement prior to RUG
- Evaluation How • Retrograde Urethrogram



#### Evaluation - Urethral Trauma







Posterior Urethral Injury RUG

#### Imaging – Urethral Trauma

- Vhen a urethral injury is suspe
- Key aspect is placement of the patient in a 30-45% lateral decubitus position to ensure adequate visualization of the
- entire urethra

  Partial injuries to the urethral lumen will reveal some
  contrast extravasation coupled with passage of a variable
  amount of contrast into the lumen of the bladder
- amount of contrast into the lumen of the filadder In complete urethral transection, a dramatic bloom of urinary contrast extravasation at either the bullbomembranous junction or the prostatic apex Another key consideration in urethral injury imaging is pattern of pelvic fracture
- Peivir fractures that produce urethral injury involve the anterior arch of the peivir ring
   Specific fractures that are associated with a greater risk of urethral injury are publis symphysis diastasis and inferior publicant infacture, especially in the medial aspect of the rami
- rami fracture, especially in the inedial aspect of the rami In patients with urethral injury accompanied by pelvic fracture, it is essential to evaluate for concomitant bladder injury

  Combined bladder and urethral injury is found in 10-29% of patients with bladder injury and pelvic fracture



#### Diagnostic Testing - Urethral Trauma

- Cystoscopy can be used to diagnose urethral injury
  - Patients taken directly to the operating room for hemodynamic instable or from penetrating trauma cystoscopy is used to inspect the urethra
- In partial urethral injury, cystoscopy can facilitate Foley catheter placement
- In patients with penetrating injuries to the posterior urethra, rectal injury should be considered
- Female patients with pelvic fracture and physical findings concerning Retrograde urethrogram is not technically feasible for the assessment of the urethra in pelvic trauma
   Best diagnostic test is cystoscopy
   Either a flexible cystoscope or special rigid scope without a cutback beak

#### Management - Urethral Trauma

- Management Catheter Drainage
  - Guideline statements 20, 21, 25
  - Establish prompt urinary drainage in patients with pelvic fracture associated urethral injury

    • A urologist may attempt a retrograde catheter placement in partial urethral injuries
  - May place suprapubic tubes (SPTs) in patients undergoing open reduction
  - internal fixation (ORIF) for pelvic fracture

     Establish prompt urinary drainage in patients with straddle injury to the
  - anterior urethra

    - (Rosenstein and Alsikafi 2006)

      Acceptable options include urethra catheter (if possible) or suprapubic cystostomy tube

#### Management - Urethral Trauma

- Management Endoscopic
  - Guideline statement 22
  - Perform primary realignment (PR) in hemodynamically stable patients with pelvic fracture associated urethral injury
  - Not perform prolonged attempts at endoscopic realignment in patients with pelvic fracture associated urethral injury

# Management - Urethral Trauma

#### Management – Urethral Trauma

- Anterior urethra
  - Management varies based on mechanism

    - Blunt urethral injuries primary objective is urinary diversion
       Diversion with either urethral Foley catheter placement or suprapubic cystostomy tube placement
    - Penetrating injuries should have immediate operative intervention
      - Low velocity gunshot or stab wound and limited tissue loss, primary surgical repair is indicated
         Performed using absorbable suture creating a spatulated primary repair
      - High velocity gunshot or significant tissue loss, urinary diversion only is performed.

#### **Urethral Trauma**

- Management Surgical
  - Guideline statement 24
  - Perform prompt surgical repair in patients with uncomplicated penetrating trauma of the anterior urethra

    - (Broghammer and Wessells 2008), (Brandes 2006)

      If feasible primary reconstruction using two layer technique with fine absorbable suture

      If damage is excessive or significant blast effect, temporary urethrostomy at site of injury
    - Delayed reconstruction of urethral defect

#### Management – Urethral Trauma

- Posterior urethra

   Variable location of injuries distally beyond the external sphincter or at the prostatic apex just proximal to the external external control of injuries distally beyond the external sphincter or at the prostatic apex just proximal to the external control of the prostate of the inner distalled goal in management of complete urethral disruption is to obtain urinary drainage, usually with the placement of a Suprapuble. Use the appropriate placement of a Suprapuble. Use of a Suprapuble use of the substance of the urethra, 3-10 days after injury, when stable of the substance of the substance
- - rostate utertra within the pews hale uterthra Repaired at time of presentation unless the patient is hemodynamically unstable due to association with vaginal laccrations
  - lacerations
    Repair is recommended during the initial hospital course to minimize the chance of post injury urinary incontinence
    or development of urethroughal fistula
    Distal female urithroughal fistula
    Substal female urithroughal substall substalling the substalling the

#### Management - latrogenic Urethral Trauma

Manipulation of catheter by Urology Placement of 3-way catheter

Cystoscopy with guidewire catheter placement Rigid cystoscopy in operating room for catheter Cystoscopic or percutaneous suprapubic tube

Laparotomy with cystorrhaphy and catheter

#### No. • Management

- 3 studies evaluated incidence of injury
- Range of 2-6.7 per 1000 catheters All patients required urologic intervention
- All patients developed short term complications
- Complications ≥ grade
  2 occurred in 81% of patients (own et al., 2016)
  4 0% of patients developed urosepsis
   Overall 14 patients
   ICU admission in 3

#### Management - latrogenic Urethral Injury (AUS)

- Traditional management is placement of Foley catheter
  - Concept is to allow for re-epithelialization of the urethra
     Many men will develop urethral stricture
- Secondary urethral healing delays surgery AUS replacement and treatment of incontinence
- Some have advocated primary repair of the urethra at time of explantation (Rozanski et al 2014), (Chertack et al, 2016
- In theory, urethral re-approximation should allow for closure of defects and mucosal apposition
- Case reports exist of leaving asymptomatic erosions in situ (Singla and Singla,
   2015)

#### latrogenic Urethral Injury - Outcomes

- Significant increase in cost and length of stay
  Total cost \$ 375,815
  Current £ 1 = \$ 1.12
  Increased length of stay
  Range 2.07 = 9.4 ± 10 days
  Poor documentation to corroborate urethral injury from catheter attempt
- Limited long term clinical data
   Davis et al 2016
   24% Suprapubic catheter
   21% Indovelling Foley catheter
   24% Perform intermittent cath
   11% Required dilation

	No.	Cost (€)	Total Cos (€)
Inpatient stay in ICU	3 (17 nights total)	2,936/Night	49,912
Inpatient stay at word level	34 (330 nights total)	832/Night	274.560
Flexible cystoscopy	13	130	1,690
SPC	12	150	1.800
Surgical theatre (open cystotomy)	1	3,000/Hr	3,000
Surgical theatre (endoscopic access to bladded)	1	3,000/Hr	1,500
Retrograde/antegrade unethrogram	2	225	500
Guidewine	17	42-70	935
Catheters	37	20-65	1,480
Total cost			335.377

Davis et al, 2016

#### latrogenic Urethral Injury (AUS) – Outcomes

- In situ urethroplasty (Ro.
- Retrospective analysis of 26 patients undergoing explantation of eroded AUS

   6 year time frame from single center experience

  - 2-0 monofilament suture is used to close the urethral defect in a single layer over 14-16 Fr Foley catheter
- Results
  Significant reduction in urethral stricture formation
  38% (5/13) vs 85% (11/13)
  No significant increase in operative time 78 vs 70 minutes
  Trend toward faster secondary procedure



#### latrogenic Urethral Injury (AUS) – Outcomes

#### latrogenic Urethral Injury – Prevention Strategies

- Education
  - Kashefi et al demonstrated 5 fold decrease with nursing education
    - 1 hour didactic session

    - 2 hour hands on skills lab
       Educational posters at nursing stations • Incidence ↓ from 3.2/1000 to 0.7/1000
  - Others have evaluated house staff education at tertiary referral

H.U.B. ert a Foley catheter Insert catheter to the hub. **1.H**ub 2. Urine Wait for urine to return. 3. Balloon Infate the balloon with sterile water.

#### latrogenic Urethral Injury – Prevention Strategies

- · Build a better catheter
  - Build a better catheter

     Human urethra is injured with increase in diameter > 40% of baseline

     Minimum required pressure:

     187 KPa = 27 PSI

     Different catheter materials transmit pressure differently (www 4, 2011)

     Silicone force > 200 KPa in the urethra

     Latex catheters > 150 KPa in the urethra

     Latex catheters > 150 KPa in the urethra

     Silicone catheter burst with ↑ pressure Syringe with safety vallye limits
- Syringe with safety valve limits pressure to 150 kPa



#### Complications - Urethral Trauma

- Monitoring Complications
  - Guideline statement 23
  - Monitor patients for complications (e.g., stricture formation, erectile dysfunction, incontinence) for at least one year following urethral injury
    - Patients are at risk for erectile dysfunction and incontinence

    - Patients are at risk for erectile dysfunction and incontinence
      Pelvic fracture urethral injury (PFUI) has a low risk of incontinence
      Pelvic fracture and damage to surrounding structures is typically the cause of erectile dysfunction and/or incontinence
      Incontinence risk 4-18%
      Frectile dysfunction risk 24-46%
      (Mouraviev, Coburn et al. 2005)

#### Complications – Urethral Trauma

- - Serious long-term sequelae often
  - Serious long-term sequelae often accompany traumatic urethral injury
     Most urethral injuries are associated with dense fibrosis in the intervening gap created by transection
     Urethropiasty is the most appropriate therapy to reestabilish patent urethra after traumatic injury
     Outcomes of posterior urethropiasty are excellent an average rate of approximately 83%
  - Other complications include diverticula formation, urinoma, or fistula to the perineum or rectum



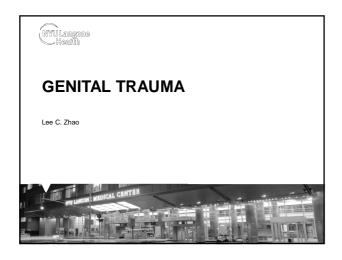
#### Complications – Urethral Trauma

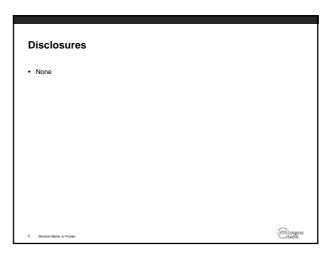
#### **Urethral Injury: Conclusions**

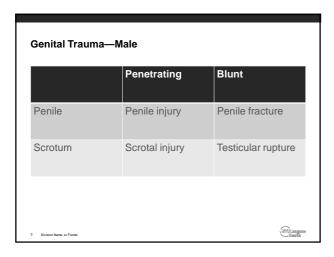
- · latrogenic Foley catheter injuries

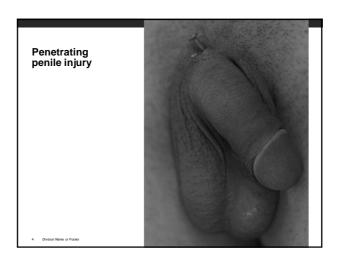
  - Result in significant increased cost and patient morbidity
     Simple education and demonstration of catheterization technique can significantly reduce incidence of injury
- Better catheter design can reduce severity and incidence of catheter related urethral injuries
- Urethral injury due to AUS erosion
  Frosion is a less common cause of urethral injury (5-10%)
  Immediate repair of significant injuries appears to result in lower incidence of complications
  Simple repair does not increase operative times

- Simple repair ubos not increase operative times
   Urethral Trauma
   Often associated with blunt injury and more common in the proximal urethra
   Key management point is establishing urinary drainage
   Patients with urethral injury from all etiologies should be monitored for at least one year for complications related to their injury.



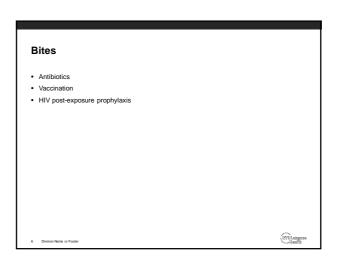


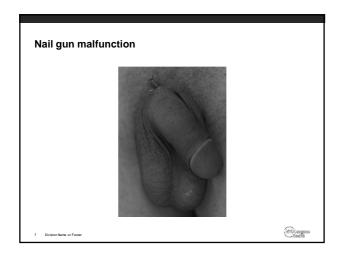


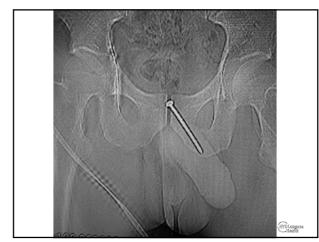


Penetrating penile injury

Evaluation: physical exam
Imaging: retrograde urethrogram if urethral injury suspected
Surgical exploration
Mechanism of injury—approach for exploration, antibiotic choice





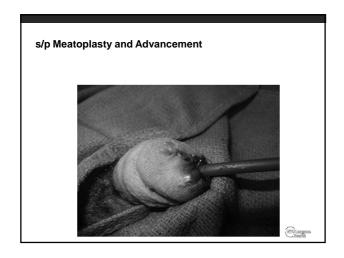




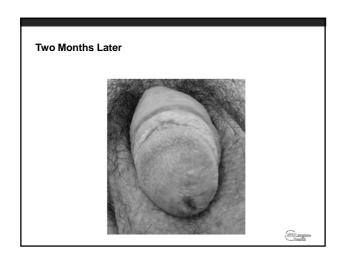




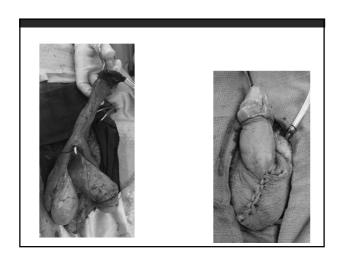


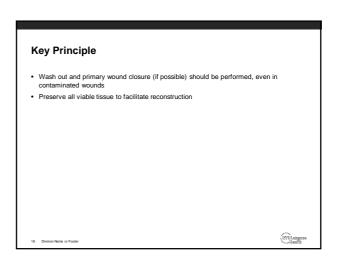






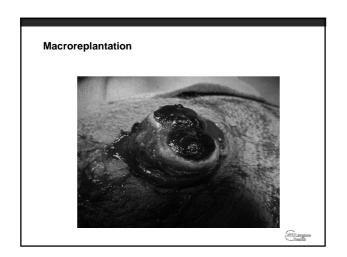






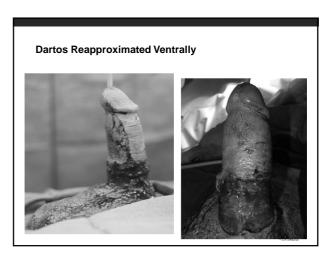








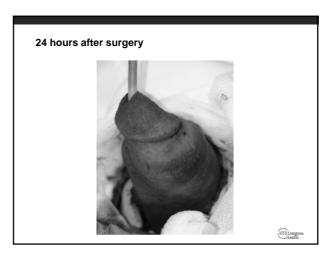


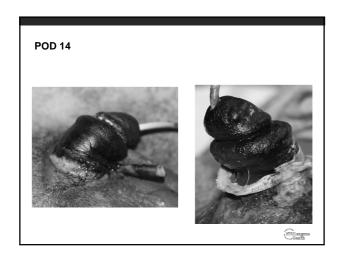


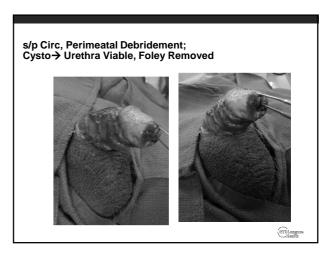




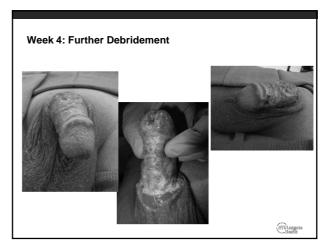




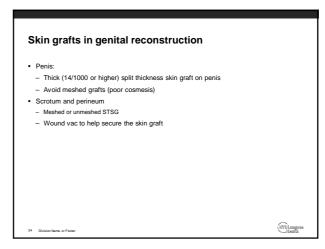




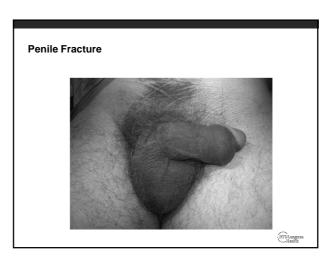










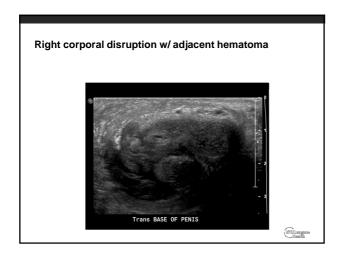


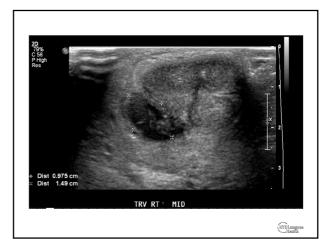
# Low vs. High Clinical Suspicion Things to consider in history and PE... Immediate detumescence Inability to achieve erections after event Severe pain Changes in corpora noted on exam Significant edema/hematoma

#### **Use of Ultrasound**

- 150 patients from Jan 1997 to Nov 2009
- Divided into two study groups based on clinical presentation and imaging results
- G1: low suspicion (25 patients)
  - All patients underwent conservative management (u/s)
- G2: high suspicion (125 patients)
- All patients underwent surgical exploration
- All patients in G1 (25 patients) underwent US
- Ruled out PF in 100%
- All managed with painkillers/anti-inflammatories without hospitalization
- 12 /125 patients in G2 -- US for "doubtful dx"
  - 9 rupture of corpus cavernosum (75%)

Koifman, et al. Urology, 2010



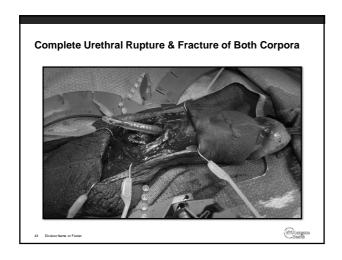




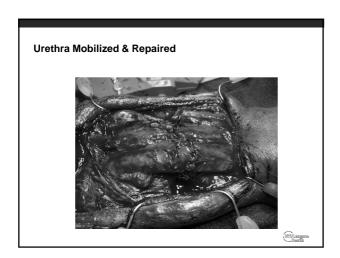
# Repair Via Penoscrotal approach

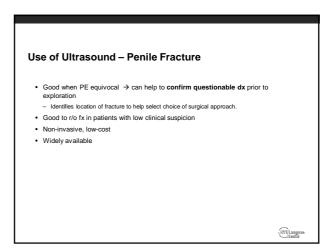
- Most fractures are ventral, at the base of penis.
- Urethral injuries almost always occur with bilateral corporal rupture
- Circumcising incision provides poor exposure to proximal corpora
- Penoscrotal approach allows use of the lonestar retractor
- If injury is completely dorsal, can convert incision into "T" and deglove

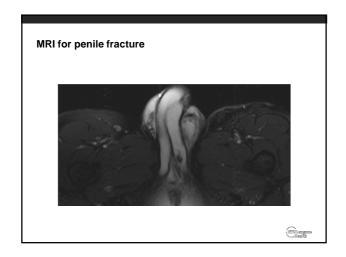
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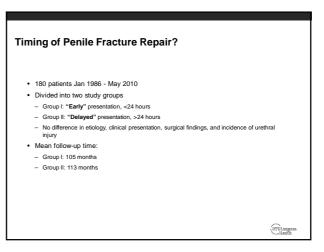












#### **Timing of Repair - Results**

- · After long-term f/u, 35 patients (19.4%) had complications:
- Pain on erection (1.4%)
- Deviation on erection (13.9%)
- Erectile dysfunction (13.4%)
- Palpable plaques (12.9%)
- NO difference in complications

El-Assmy, et al., 2011



#### **Timing of Repair**

- Patients presenting up to 7 days after penile fracture can be managed surgically with similar outcomes to patients with immediate repair
- US showed site of tear in 53/58 (93%)

El-Assmy, et al., 2011



#### Exploration 5 days after injury





#### Corporal repair



#### Scrotal injury

- Penetrating
- Exploration if dartos is violated
- Ultrasound controversial
- Blunt
- Ultrasound to evaluate testicular rupture
- Exploration for testicular rupture

29 Division Name or Ecotor



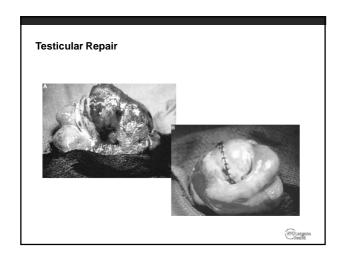
#### Ultrasound

- Heterogeneous echo of testicular parenchyma with loss of contour
- Tunica albuginea rupture



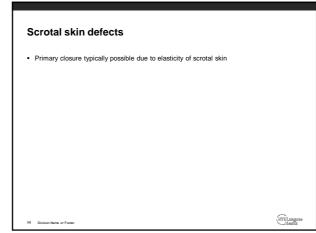
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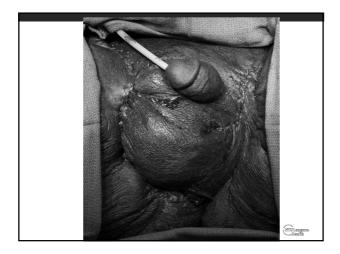


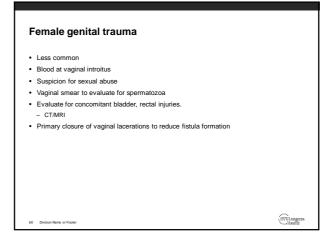












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Injury	Screening Imaging	Intervention
Penis (blunt)	Ultrasound/MRI	Immediate Repair (up to 1 week)
Penis (penetrating)	None vs CT	Immediate Repair
Scrotum	Ultrasound	Repair vs observation
Vas deferens	Intraop finding	Ligate Vas, Delayed VV
Anterior Urethra (usually associated w/ penis or scrotum)	RUG	Immediate Urethroplasty

Immediate	Conservative
Penile injury (fracture, penetrating)	Blunt penile injury without fracture or urethral involvement
Penetrating scrotal injury	Blunt scrotal injury without testicular injury
Blunt scrotal injury w testicular involvement	
Anterior urethral injury	
	HVV Langano Hearth



# Management of Upper Urinary Tract Obstruction

Stephen Y. Nakada, MD

#### **Disclosures**

Stephen Y. Nakada, MD. FACS, FRCS (Glasg.)

• Boston Scientific - Consultant



#### **Upper Tract Obstruction**

- Evaluation of Upper Tract Obstruction
- Ureteropelvic Junction Obstruction
- Retrocaval Ureter
- Ureteral Stricture Disease
- Ureteroenteric Anastomotic Stricture
- Retroperitoneal Fibrosis

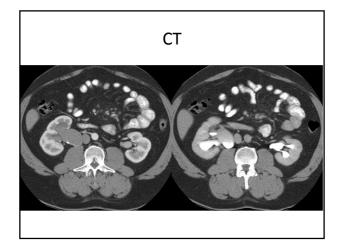
#### **Upper Tract Obstruction**

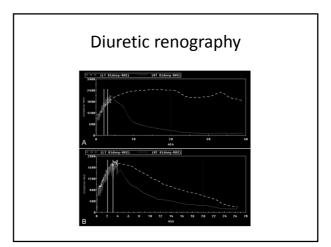
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#### **Evaluation of UTO**

- CT- low dose, CT urography
- IVU
- Ultrasound
- Retrograde pyelogram
- Diuretic Renography
- Whitaker test







#### Whitaker Test

- Useful with concomitant stones
- Ultimately accurate
- Requires NT and foley catheter
- Must be dynamic

#### **Upper Tract Obstruction**

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#### **Ureteropelvic Junction Obstruction**

- Intrinsic, aperistaltic segment
- Role of crossing vessels
- Diagnosis: renography, CT angiography, CT urography
  - Roles for crossing vessel, UPJ anatomy
  - Ultrasound; prenatal value and multicystic kidney
- Renography
  - Quantitative, functional status, follow up

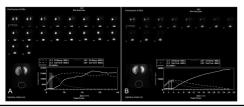
#### **UPJ Etiology**

Lack of Interstitial cells of Cajal Aperistaltic segment Congenital TGFB, EGF. NO as causes



#### **UPJO: Indications**

- Symptomatic obstruction
- Impairment of renal function
- Stone disease or UTIs
  - Causal hypertension

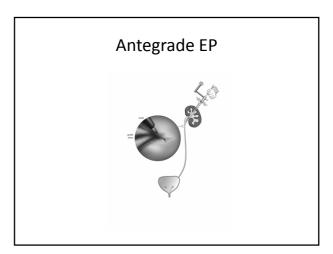


#### **UPJO-** Intervention

- · Dismembered pyeloplasty
- Endopyelotomy
- Laparoscopic pyeloplasty
- Robotic assisted laparoscopic pyeloplasty (RALP)

#### **Endourologic Mgt for UPJO**

- Endopyelotomy
  - Antegrade
  - Retrograde
- · Crossing vessels
  - Data suggest success rates altered by CV, degree of hydronephrosis
  - Requires high-dose axial imaging or angiography
- Concomitant stones
  - Antegrade approach favored



# Retrograde EP

#### **UPJO** with stones

- PCNL and antegrade endopyelotomy
  - Concerns of inflammation at the UPJ
  - Need to assess UPJ once stone removed
  - Option for Whitaker test with existing NT

#### Secondary interventions

- Open or lap/robotic for failed endopyelotomy
- Endopyelotomy for failed open or lap/robotic
  - Data quite good (>90%) for EP following pyeloplasty

#### **Pyeloplasty**

- Open
- Laparoscopic
- Robotic

#### **Open Pyeloplasty**

- Flank incision
- 95% success rate
- Effective in children
- Dorsal lumbotomy approach in select cases
- In adults, an approach in centers lacking MIS expertise

#### Laparoscopic Pyeloplasty

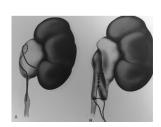
- Pioneered by Kavoussi
- Success rates >90%
- Requires laparoscopic suturing, knot-tying
- Optional mesenteric approach
- Eliminates concerns of crossing vessels
- Allows for management of stones concominantly

#### Robotic pyeloplasty

- Logical extension of the procedure from laparoscopy
- Allows more surgeons to perform the procedure
- Opens options for single incision
- Similar operations and approaches to repair UPJ; Success guivalent
- Cost

#### **UPJ** repairs

- Dismembered
- Foley YV plasty
- Fenger plasty
- Vertical flap



#### Ureterocalicostomy

- Options for UPJO and PUS with small renal pelvis
- Also for HSK for dependent drainage
- Well accepted salvage procedure
- Assess function of ipsilateral moiety



#### **Upper Tract Obstruction**

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- Retroperitoneal Fibrosis

#### Retrocaval Ureter

- Rare anomaly, persistence of the lower cardinal veins during embryologic development
- · Diagnosis by CT
- Treatments
  - If indicated, open or robotic approaches successful

#### **Upper Tract Obstruction**

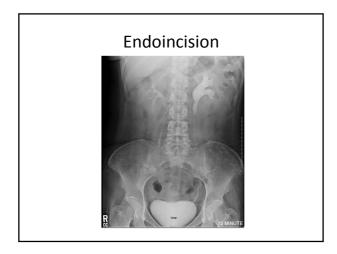
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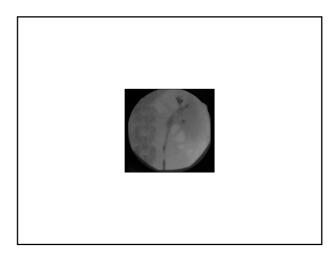
#### **Ureteral Strictures**

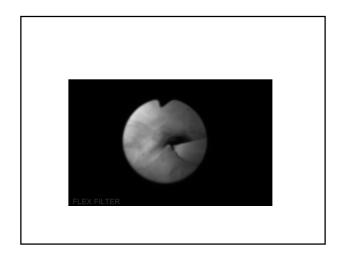
- Diagnosis
  - Retrograde pyelogram
  - Diuretic renography with split function
- Indications
  - Symptoms, infections
  - Renal functional loss
  - up to 2 cm managed endoscopically
  - 20% function

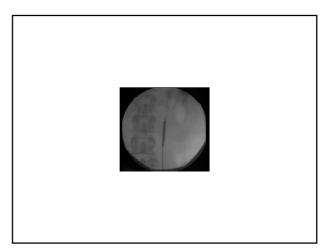
#### Treatment options

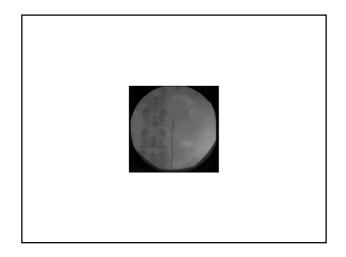
- Balloon dilation- low longterm success
- Endoscopic incision
  - Laser
  - Cold knife
  - Cutting balloon catheter (less used due to risk of bleeding and improved lasers)

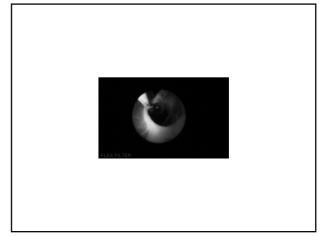


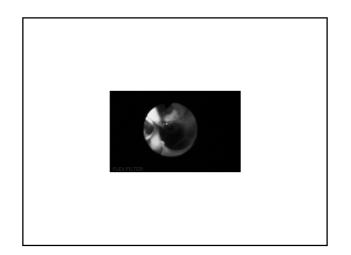


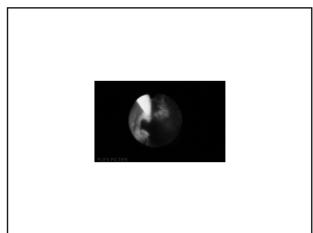


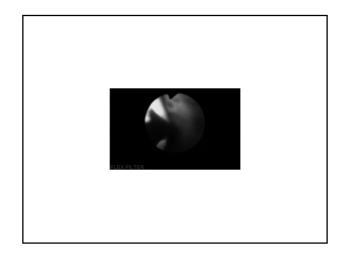


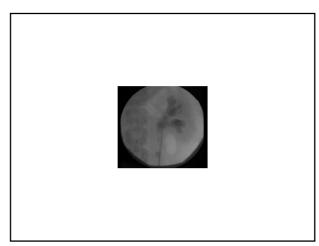


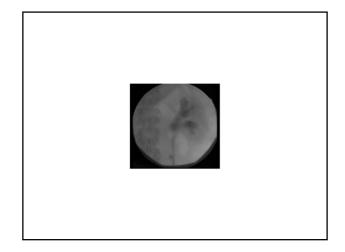


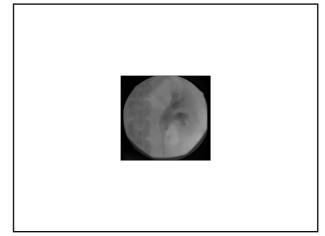


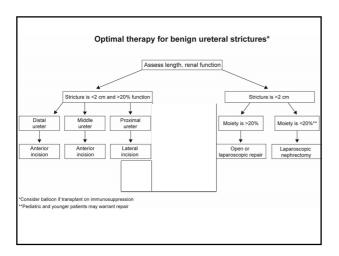










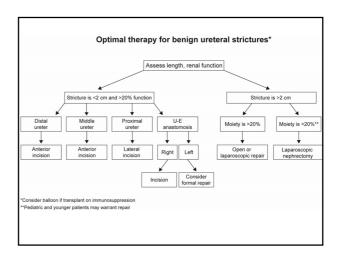


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- Retroperitoneal Fibrosis

#### **UE Strictures**

- Success rates poor bilaterally
- Right side better than left
- Assess for TCC
- Always do a renal scan
- Retrograde procedures challenging



#### **Bridging Longer defects**

- Ureteroneocystotomy
- Boari flap
- Ureteroureterostomy
- Trans UU
- Ileal ureter
- Autotransplantation



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#### Retroperitoneal Fibrosis(RPF)

- Presentation-inflammatory disease in the RP causing compression of the structures including the ureters, L4-5
- 70% idiopathic, but it is considered a chronic periaortitis, a large vessel vasculitis
- 30% of patients have a cause, such as methysergide use, ergot alkyloids, B blockers, or malignancy

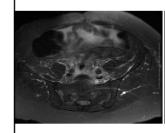
#### **RPF** evaluation

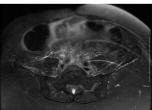
- ESR, CRP elevation in aortitis group 30-50%
- CT reveals hydronephrosis
- Renal scan
- MRI low signal intensity on T1, higher in active disease on T2
- Gadolinum enhancement a sign of active disease
- PET scan

#### CT diagnosis



#### MRI





#### **RPF Management**

- Decompression, stent or NT when symptoms of obstruction
- Postobstructive diuresis a concern
- · Medical management
  - Steroids 80% response, follow ESR, CRP,MRI
  - 2 year therapy typically, remove drains, then taper
  - Immunosuppressive agents are second line, as 50% of steroid responsive cases recur during tapering
    - Cyclosporine, cyclophosphamide, azathioprine

#### Surgical Management PRF

- Ureterolysis
  - Mass biopsies
  - TP approach
  - Intraperitoneal placement of the ureters
  - Omental wrap
- Open, lap or robotic
  - Good success up to 90% at 30 months
  - Lap equal to open with shorter recovery
  - Robotic also reported, 84% with shorter recovery
- Autotransplantation

### **Evaluation and Management of the Kidney Stone Patient: an Update**

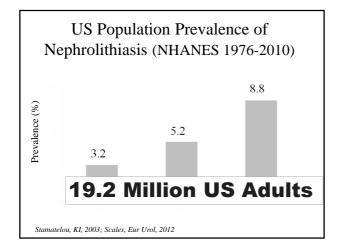


David S. Goldfarb, M.D. david.goldfarb@nyumc.org

#### Disclosure

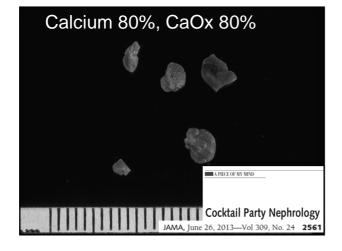
- · Consultant:
  - Allena, Alnylam, Retrophin, The Ravine Group
- PMHx: CaOx stones

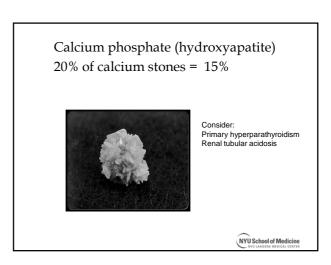
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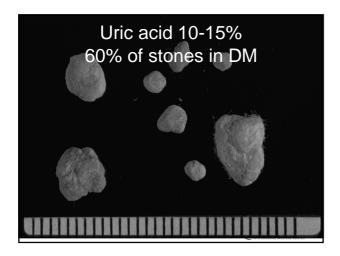


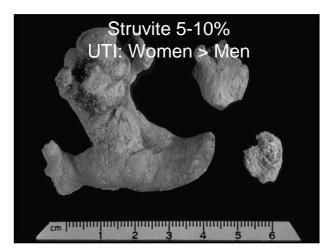
#### Prevalence and Recurrence of Stones

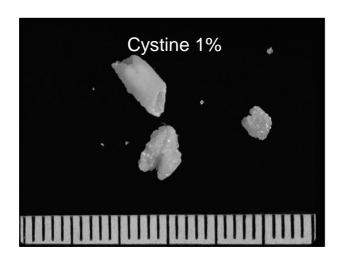
- Lifetime prevalence:
  - 12% in American men
  - -7% in American women
- Recurrence rates:
  - -30% at 5 years
  - -50% at 10 years
  - -80% at 20 years



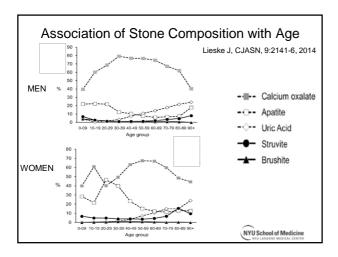








Calcium oxalate	29,319	<b>47.0</b>
A C'C		67.3
Apatite	7000	16.1
Uric acid	3611	8.3
Struvite	1318	3.0
Brushite	374	0.9
Cystine	151	0.35
Ammonium urate	105	0.20
Artifact	1393	3.2
Other	171	0.4
Drug	60	0.1
	42	0.1
Dihydroxyadenine	1	0.002
Other Drug Sodium/potassium urate	171 60 42	0.4 0.1 0.1



Urinary Risk Factors for Calcium Stone Disease Hypercalciuria

- Hyperoxaluria
- Hypocitraturia
- Hyperuricosuria
- Low urine volume
- (too much crystal promoters)
- (too little crystal inhibitors)

#### **AUA Guidelines**

#### Medical Management of Kidney Stones: AUA Guideline

Margaret S. Pearle, David S. Goldfarb, Dean G. Assimos, Gary Curhan, Cynthia J. Denu-Ciocca, Brian R. Matlaga, Manoj Monga, Kristina L. Penniston, Glenn M. Preminger, Thomas M. T. Turk and James R. White

http://www.auanet.org/education/guidelines/management-kidney-stones.cfm

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# **Evaluation of Patient with First Stone Episode**

- **History:** medications, occupation, family history of stones or other kidney disease (e.g. PKD), inflammatory bowel disease (e.g., Crohn's disease).
- **Diet:** intake of protein, purines, sodium, fluids, oxalate, and calcium
- Imaging: are there other stones present?
  - Or anatomically important kidney disorders, e.g. PKD, MSK

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### **Evaluation of Patient with First Stone Episode**

- Serum:
  - Electrolytes, creatinine
  - Hypercalcemia, values > 10.0 mg/dl
    - Consider:
      - primary hyperparathyroidism
      - Sarcoidosis
      - CYP24A1 mutations and vitamin D intake
  - $-[HCO_3] < 22 \text{ meg/L}$ 
    - Consider distal renal tubular acidosis
  - Mg, PO<sub>4</sub>, uric acid

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## **Evaluation of Patient with First Stone Episode**

- Urinalysis:
  - high urine pH: RTA
  - high urine pH: struvite stones
  - low urine pH: uric acid stones
- · Urine culture if indicated
- Stone analysis (OR do qualitative cystine screening at least once in children-age 50)
  - X-ray diffraction
  - Infrared spectroscopy

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#### **Medications and Stones**

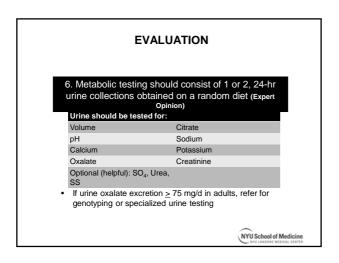
- · Topiramate, acetazolamide
- Atazanavir
- Vitamin C
- Felbamate
- Triamterene
- Guafenesin

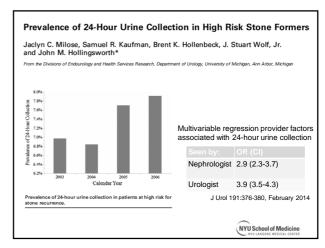
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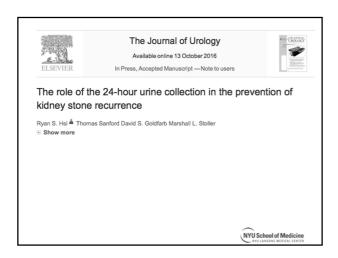
#### **EVALUATION**

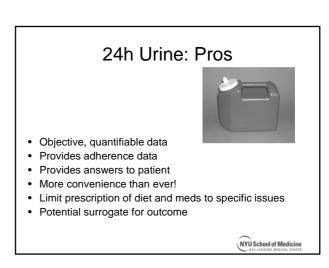
5. Clinicians should perform additional metabolic testing in high-risk or interested first-time stone formers and recurrent stone formers (Standard: Grade B)

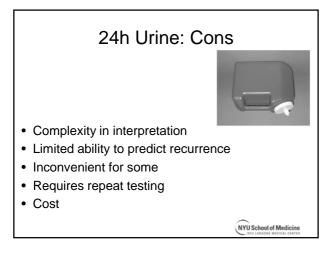
Grade B evidence: "moderate"

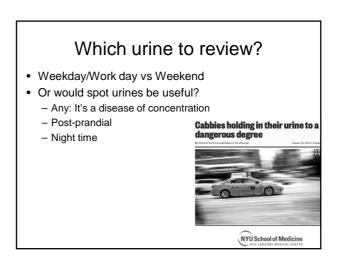


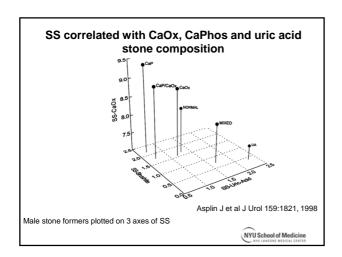


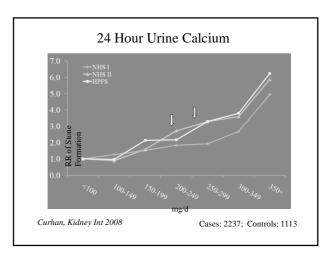


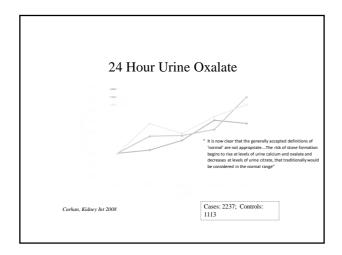


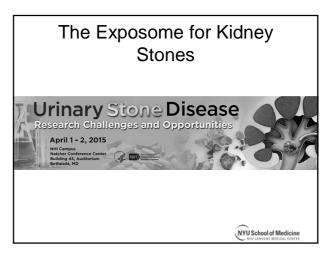


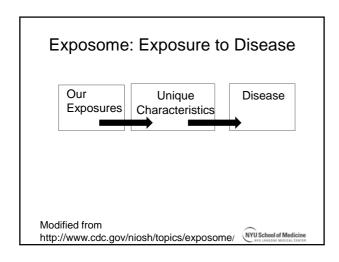


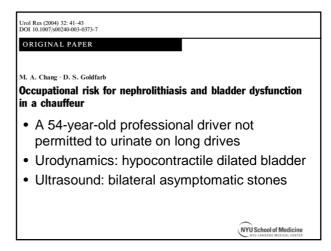




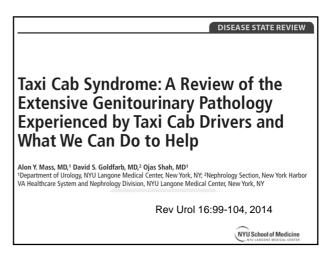


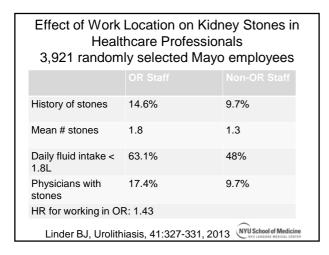


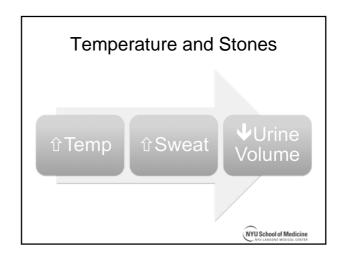


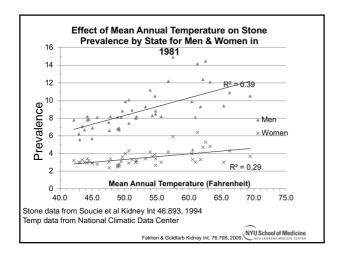


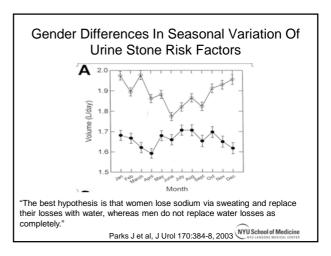


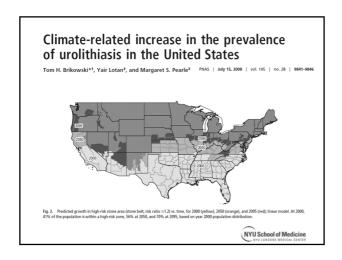


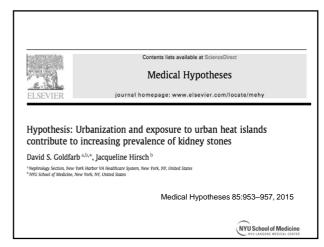


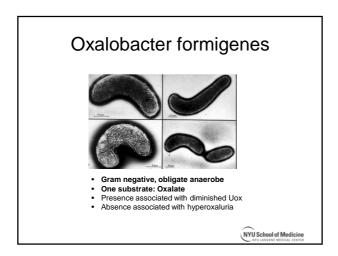


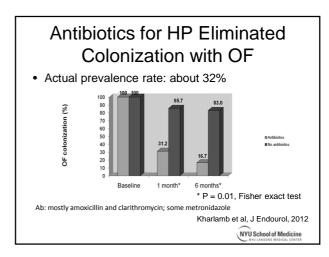


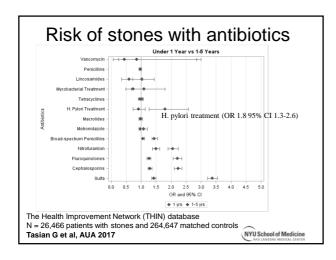


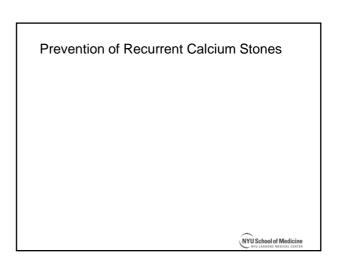


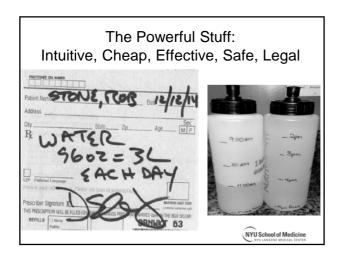












# Non-specific Prevention of Calcium Oxalate Stones

- Increase urine volume to > 2 liters/d
- Supported by RCT
- Emphasis on output, not intake
  - more with heat, exercise
- All day long
- Before sleeping
- Coffee and beer are protective!

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What is the treatment for low urine volume? What is the treatment for occupational kidney stones?

#### Potassium citrate:

• Surgeon: before going to the OR

• Baseball player: before going on the field

Teacher: before class

· Cab driver: before getting into the taxi

• Steel worker: before entering work place

• Everyone: at bedtime

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#### Diet: Relative risk of symptomatic kidney stones according to dietary calcium intake

Calcium	< 605	605-722	723-848	849-1049	> 1050
RR stones	1.0	0.71	0.64	0.61	0.56

N =45,510 men

Curhan NEJM 328:833, 1993

Similar result in women: Curhan, Ann Int Med 126:497, 1997

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#### Increasing Dietary Calcium Intake for Prevention of Ca Stone Recurrence

- Borghi et al NEJM 346:77 (2002)
- 60 men in each arm: men with at least 2 episodes of calcium stones and hypercalciuria (>300 mg/day)
- 1) "normal" amount of calcium (30 mmol per day) but reduced amounts of animal protein (52 g per day) and salt (50 mmol of sodium chloride per day)
- 2) traditional low-calcium diet, which contained 10 mmol of calcium per day
- Outcome: stone recurrence either silent or symptomatic

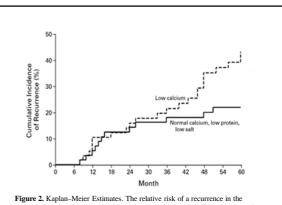


Figure 2. Kaplan–Meier Estimates. The relative risk of a recurrence in the group assigned to the normal-calcium, low-protein, low-salt diet, as compared with the group assigned to the low-calcium diet, was 0.49 (95 percent confidence interval, 0.24 to 0.98; P=0.04).

#### **Prevention of Calcium Oxalate Stones**

- · Calcium restriction is out!
- Not proven to reduce stone recurrence
- · Associated with bone demineralization

Calcium intake 800-1200 mg per day

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#### Pharmacologic therapy: thiazides

- Chlorthalidone (indapamide)
- Lower salt intake
- Supplement with K citrate
  - -NO triamterene (e.g. Dyazide, Maxzide)
  - Amiloride 5-10 mg once or twice a day for K sparing
  - -Spironolactone

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#### Other benefits of thiazides

- · As effective as any other class for HTN
- · Cheaper!
- Best drugs for HTN in the elderly
  - For systolic HTN
- · Associated with increased bone density
  - Fewer fractures

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#### **Thiazides**

- If UCa shows no "cut-point" AND
- Thiazides are effective no matter the UCa....
- · AND drugs are
- · Effective
- · Inexpensive
- · Increase life expectancy
- Increase BMD and reduce fracture rate....
- · Why not just give them to everyone

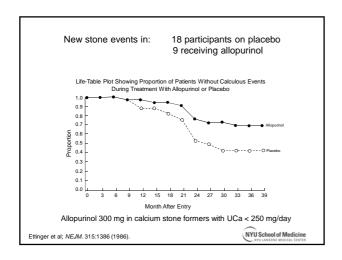
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## Drug Therapy Calcium Oxalate Stones

- Hypocitraturia
  - -Potassium citrate: 20-40 meq bid
  - -NOT sodium citrate: inc. UCa
  - -Use in "non-selected" cases

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# Effect of Potassium Citrate on Bone Density, Microarchitecture, and Fracture Risk in Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial The second Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial The second Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial The second Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial The second Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial The second Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial The second Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial The second Healthy Older The second Healthy Older Adults without Osteoporosis: A Randomized Controlled Trial The second Healthy Older The second

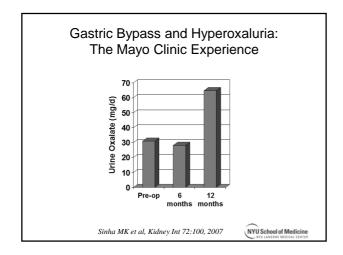


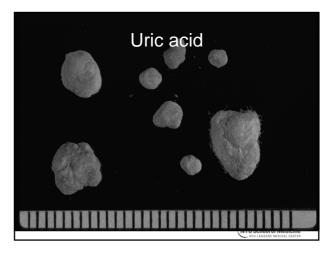
#### Hyperoxaluria

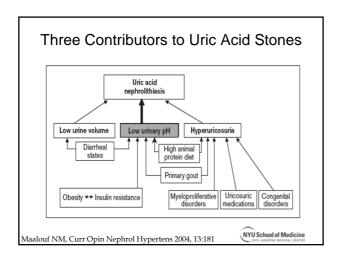
- Oxalate is an important determinant of SS
- Yet no study of the effect of lowering urinary oxalate excretion on stone outcomes has been performed
- · Increase dietary calcium intake if low
- Allena-177: oxalate decarboxylase

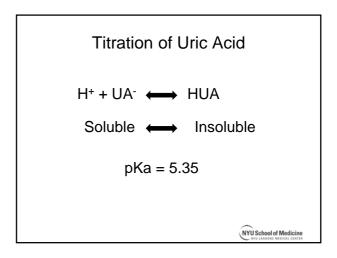


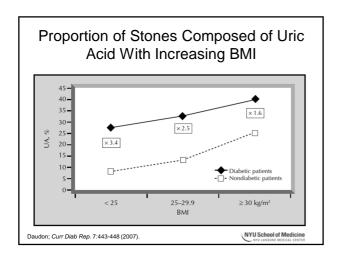
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#### **Etiology of Uric Acid Stones**

- Insulin resistance → impaired ammoniagenesis
- Impaired ammoniagenesis → "unduly acid urine"

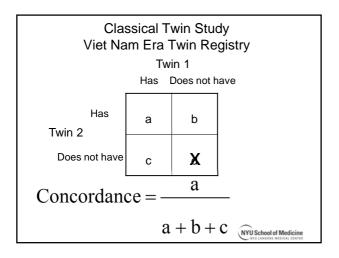
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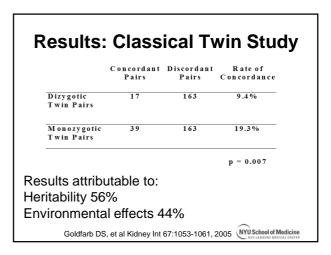
#### Treatment of uric acid stones

- · Alkalinize urine with potassium citrate
- Na citrate, NaHCO<sub>3</sub> if necessary
- Allopurinol is ineffective if UpH is not increased: reserve for patients with recalcitrant stones, difficulties alkalinizing

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NYU LANGONE MEDICAL CENTER

		During Rx
	#/1000 pt-yrs	#/1000 pt-yrs
Stones	1752	382
Urologic Intervention	198	106
Hospitalization	375	90
\$/1000 pt-yrs	\$4.5M	\$1.3M





#### Kidney Stones in Women and Men: Washington State Twin Registry

	MZ Women	DZ Women	MZ Men	DZ Men
Concordant	21	5	20	5
Discordant	159	188	75	51
Concordance	0.21*	0.10	0.35*	0.16

Heritability 45% in women, 66% in men, \*p < 0.05.

Goldfarb DS, Noonan C, Goldberg J, ASN 2012

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#### **Genetics of Calcium Stones**

- Gene responsible for hypercalciuria is NOT:
  - -Vitamin D receptor
  - -Interleukin-1 Receptor
  - -CLCN5
- Some data for SNPs of:
  - -CaSR
  - -TRPV5
  - -CLDN 14, 16, 19

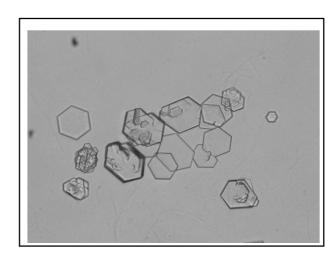
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Dawn Milliner, MD (PI) John Lieske, MD David S. Goldfarb, MD Lada Beara-Lasic, MD Viðar Eðvarðsson, MD Runólfur Pálsson, MD

Mayo Clinic: PH Mayo Clinic: Dent

New York University: Cystinuria New York University: Dent disease Landspitali Univ Hosp: APRTd Landspitali Univ Hosp: APRTd



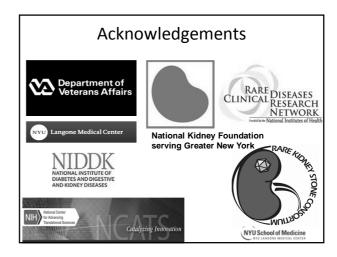
Pediatr Nephrol. 28:1923-42, 2013

REVIEW

Hereditary causes of kidney stones and chronic kidney disease

Vidar O. Edvardsson • David S. Goldfarb • John C. Lieske • Lada Beara-Lasic • Franca Anglani • Dawn S. Milliner • Runolfur Palsson

- Cystinuria
- Primary Hyperoxaluria
- APRT deficiency: Dihydroxyadenine Stones
- Dent disease



#### Surgical Management of Urinary Stone Disease

Peter L. Steinberg, MD Beth Israel Deaconess Medical Center Director of Endourology and Kidney Stone Management August 6th, 2018

#### **Disclosures**

- · No financial disclosures
- · No conflicts of interest

#### **Learning Objectives**

- · Describe a general approach to the operative management of urinary stones
- Discuss the pros and cons of ureteroscopy versus shockwave lithotripsy
- · Understand the indications for PCNL

#### **Excellent Reference**

"Surgical Management of Stones,"

2016 AUA and Endourological Society Guideline

#### Overview

- Discussing choice of surgical therapy for different stone sizes and locations
- · Indications for surgery
- Timing of surgical intervention
- Management of ureteral and renal stones:
  - SWI
  - URS
  - PCNL

## Kidney Stone Epidemiology

(Pearle 2007, Goldfarb 2009; Scales 2012; Krambeck 2014, AUA 2

- Prevalence: Appx 10% of adults
- 5.3 billion dollars annually (total cost)
- Incidence 1% of the workforce annually
- 50% second stone in 5-10 years
- Nearly 10-20% require surgery

#### Indications for Surgery

- Ureteral Stones
  - Failure of observation
  - Intractable symptoms
  - Large stone with low chance of passage
  - Prior decompression without stone passage
  - Travel or other obligations prohibitive
  - AKI

- Renal Stones
  - Large stones
  - Symptomatic
  - Want to avoid colic/passage
  - Travel or professional obligations
  - Nidus for infections
  - AKI

#### Factors in Choosing Approach

- · Location, location, location
  - Ureter: proximal, middle, distal
  - Kidney: pelvis, calyx, lower pole
- Size
  - -<1cm, 1-2 cm, >2 cm
- Stone characteristics
  - Ca ox monohydrate, uric acid, struvite
- Urinary anatomy
  - Caliceal tic, UPJ-O, urinary diversion

#### Surgical Techniques

- Shockwave lithotripsy (SWL)
- Ureteroscopy (URS)
- Percutaneous nephrolithotomy (PCNL)
- · "Open Surgery"
  - Often done with laparoscopy or robotics
  - Anatrophic nephrolithotomy, ureterolithotomy, pyelolithotomy

#### **Timing of Surgical Management**

- Acute Management
  - Emergent decompression
  - PCN or Stent
- Semi-elective management
  - Usually ureteral stones
  - Previously stented or PCN placed
- · Elective management
  - Usually renal stones

#### **Emergent Decompression**

- · Intractable pain
- Renal failure
- SIRS/Sepsis
- Solitary kidney

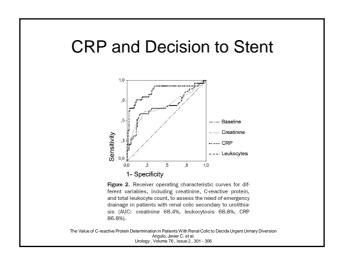


Draw MD, Kutikov et al 2012

#### Stent vs PCN

(Lipkin BJU 2013)

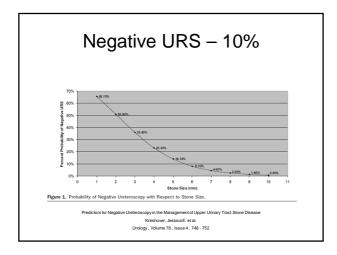
- · Dealer's choice
- Failure rate is 2% (3/130)
- · PCN associated with
  - Large stone
  - Longer ICU and hospital stay
- 90% of patients need definitive stone surgery
  - Average of 30 days after decompression



#### **Ureteral Stones**

AUA Guidelines 2016

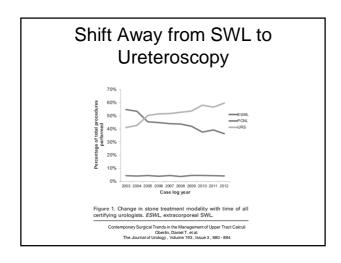
- As a rule of thumb:
  - Smaller stones pass at higher rates than larger stones
  - Distal stones pass at higher rates than proximal
- Of stones that pass, 95% pass in 30-40 days of presentation



#### **Ureteral Stone Management**

Ann Emerg Med 2007, Lotan 2002

- Distal stones = Ureteroscopy
  - SWL less of a role
- Upper ureteral stones: SWL or URS
  - SWL in good candidates
- Large proximal stones/impacted stones
  - Antegrade/PCNL
  - Lap/robotic ureterolithotomy
    - Aberrant anatomy, failures, concurrent procedures



#### SWL vs URS -- Ureteral

- SWL has less morbidity
  - Usually no stent
  - Ureteral injury not possible
- URS has a greater stone free rate per procedure
  - Laser lithotripsy is more effective than SWL
  - Greater morbidity

## SWL vs URS

- Seven RCT's (only 3 with adequate description of randomization)
- 1205 subjects
- RR stone free SWL 0.84 (CI 0.73-0.96)
- RR complications SWL 0.54 (CI 0.33-0.88)
- RR re-treatment SWL 6.18 (3.68-10.38)

#### **Distal Ureteral Stones**

- URS
  - Semi-rigid URS has a 97-98% success rate
  - Stones > 10 mm median 95% success
- SWL
  - 70-75% median success for distal stones
- Unless patients refuse URS or cannot have URS, it should be considered first line for distal stones

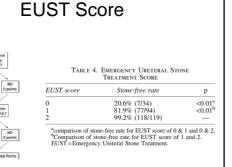
#### **Upper Ureteral Stones**

Ng, J Urology 2009

- SWL in appropriate candidates
  - Size < 1 cm
  - Hounsfield Units < 800
  - Skin to stone distance < 9-10 cm
- Stone free rate (SFR) can be > 90% with good patient selection
  - SFR declines to 50-70% in candidates without good characteristics
- URS consistently offers 80-90% SFR

#### When Will URS Fail? (Tran 2017)

- · Attempting URS on a ureteral stone carries a small risk of failure - 10-20%
- · Change in serum creatinine and periureteral inflammation can predict such failures
- Change in Cr > 0.3 mg/dL
  - Important for pre-operative counseling
  - Need to explain a second procedure may be required



#### Renal Stones

- Renal anatomy
- Stone composition
- Stone size
  - Decision for PCNL
- · Observation, URS, SWL, PCNL

#### **Renal Stones**

Steinberg/Hoenig, Smith's Endourology, 3<sup>rd</sup> ed Pais, 2015

- Appx 20-25% need surgery over 3 years
- Lower pole stones are less likely to become symptomatic over 3 years of follow-up
  - -24% versus other locations 40%

#### Can observe many stones < 1 cm

#### Renal Stones < 2 cm

Steinberg/Hoenig, Smith's Endourology, 3<sup>rd</sup> ed AUA Guidelines 2016

- SWL or URS
  - URS better SFR; more morbid
- Clearance of 80-90% feasible
- Lower pole
  - Clearance less than other locations (60-70%)
- PCNL almost 100% success but morbid

#### Lower Pole Stones 1-2 cm

- Lower Pole I Study
  - Randomized trial of SWL vs. PCNL
  - PCNL > 90% clearance and 6% 2<sup>nd</sup> procedure
  - SWL 25% clearance
- URS vs. PCNL (Pearle 2005)
  - URS 37% vs. PCNL 71% clearance
  - Unfavorable anatomy PCNL
  - Favorable anatomy consider URS

## Extracorporeal Shock Wave Lithortripsy of Lower Calya, Calcul: How Much is Treatment Outcome Influenced by the Anatomy of the Collecting Systems.

#### Renal Stones > 2 cm = PCNL

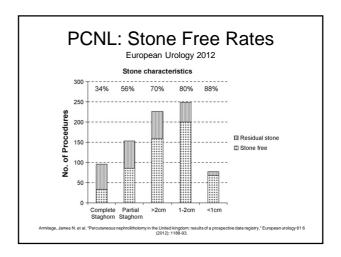
- · SWL and URS can be done
  - SFR are poor compared to PCNL
  - Residual fragments are the norm

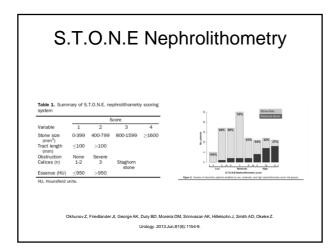
#### URS > 2 cm Renal Stones

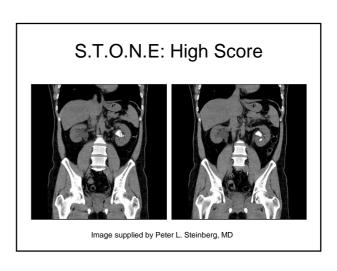
- Hyams et al 2010 120 patients
  - -86% single procedure
  - Stone free < 50%; < 4mm in 83%
- Breda et al 2008 15 pt's
  - All two stages (mean 2.3)
  - All but one stone free on US
- Hyams/Shah 2009 20 PCNL/19 URS
  - -89% vs 47% clearance (PCNL to URS)
  - Cost 1/3 for URS

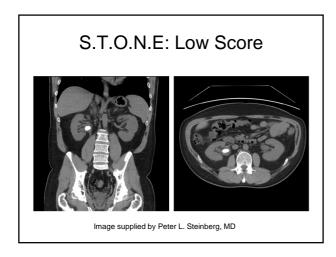
#### **URS for Larger Stones**

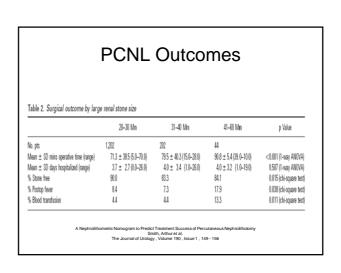
- · Distinct patient preference
- · Substantial co-morbidity in the patient
  - Pulmonary disease
- · Anatomic issues
  - Size
  - Positioning
  - Abnormal renal location/anatomy









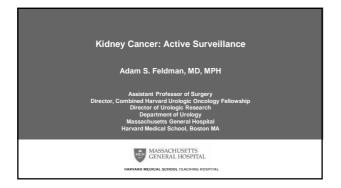


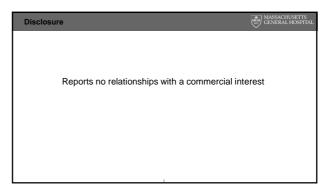
### Lap/Robotic Stone Management

- Concomitant stricture disease
- Concurrent lap/robotic procedure
- Failed URS, SWL, PCNL
- Aberrant anatomy
- Overall, these approaches are infrequently needed with today's techniques

#### Summary

- URS more effective than SWL
- SWL less morbid than URS
- Distal ureteral stones = URS
- Choose SWL candidates wisely
- PCNL for stones > 2 cm





Agenda

1. Small renal mass and RCC – epidemiology, pathology and staging
2. Treatment options for the small renal mass
3. Renal mass biopsy
4. Active treatment options – partial nephrectomy, nephrectomy, ablation
5. Active surveillance
6. Future directions – biomarkers

Epidemiology

In the U.S. in 2018 there are estimated to be:

• 65,340 new cases and 14,970 deaths from kidney cancer

Proportion of RCC found as incidental renal masses has increased from 10% in 1970's to now over 50%

Classic Triad (not commonly seen anymore)

• flank pain

• hematuria

• palpable mass

Male to Female ratio 2:1

Renal masses

85% of all renal tumors are RCC

Other malignant primary renal lesions in adults – TCC, sarcoma, lymphoma

Benign renal lesions – oncocytoma, angiomyolipoma, mixed epithelial stromal tumor (MEST), adenoma

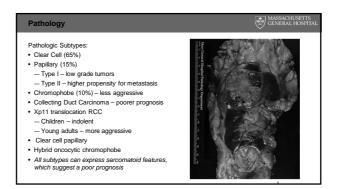
RCC Risk Factors:

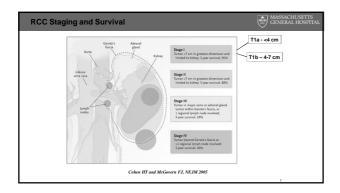
• Environmental: Smoking and Obesity

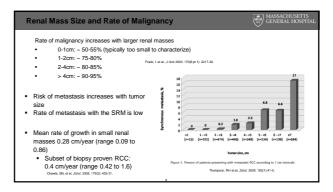
• HTN

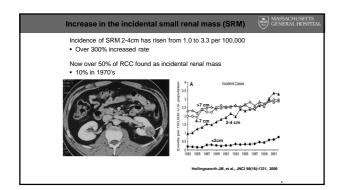
• Family History in first degree relative

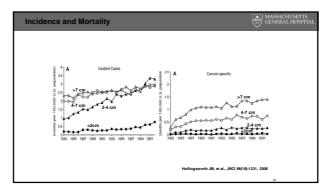
• Genetic Syndromes: von Hippel-Lindau (VHL), hereditary papillary RCC, Birt-Hogg-Dube Syndrome, Tuberous Sclerosis Complex, Hereditary Leiomyoma-RCC

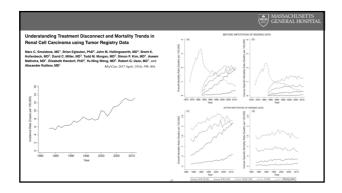


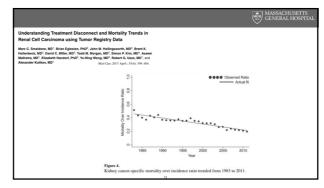


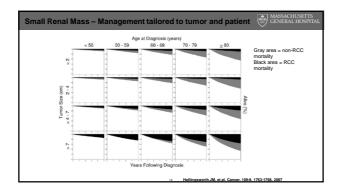


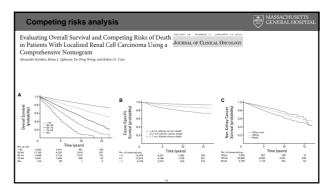


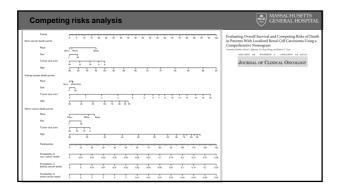


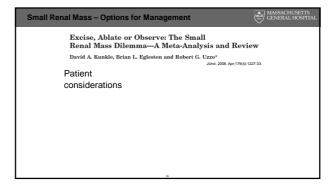


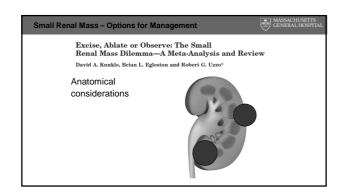


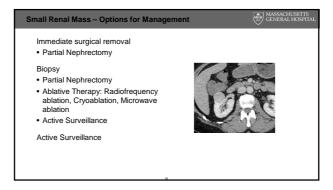


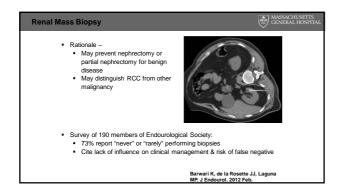


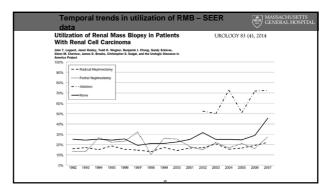


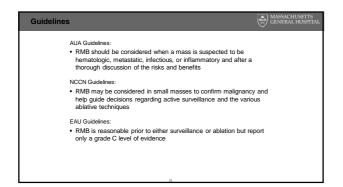


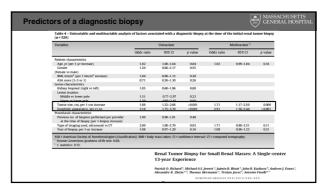


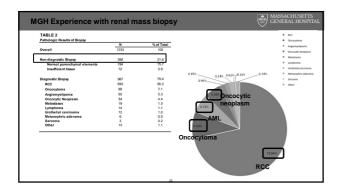


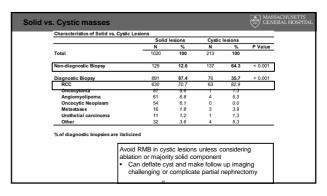


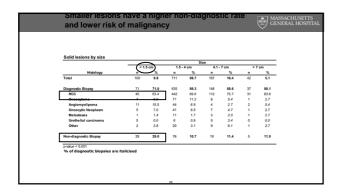


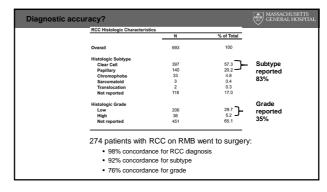


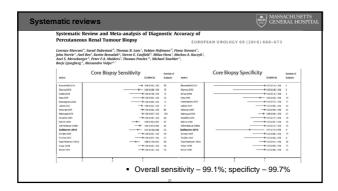


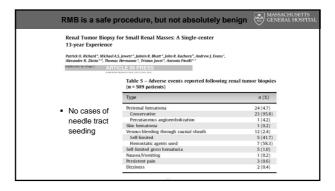


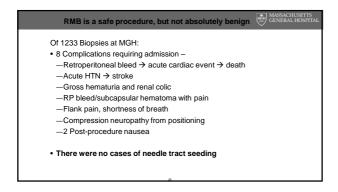


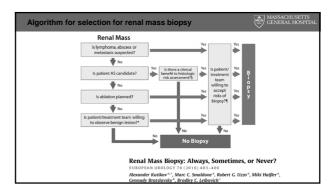


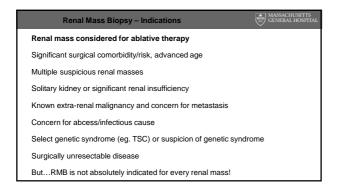


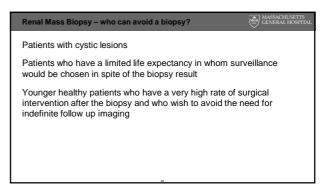


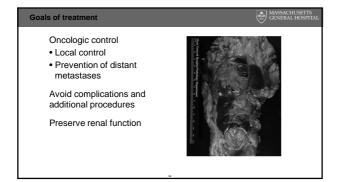


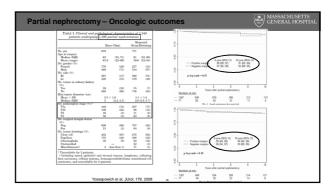


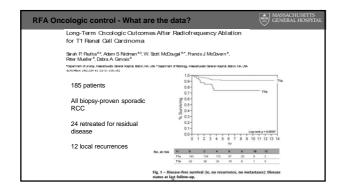


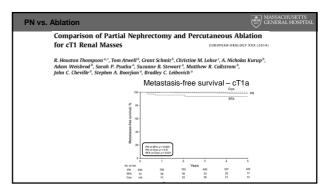


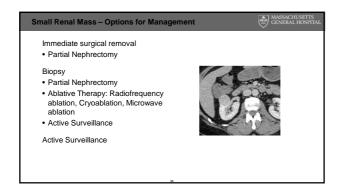


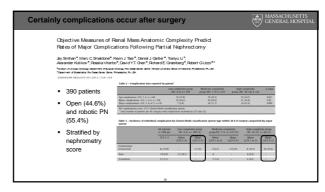


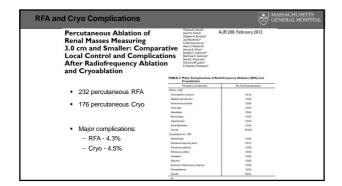


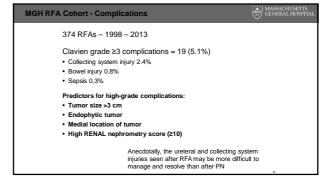


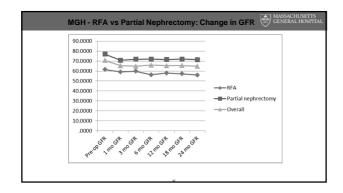


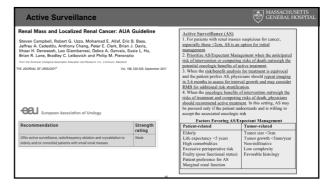


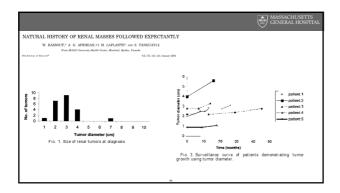


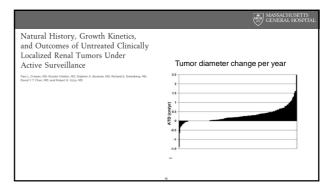


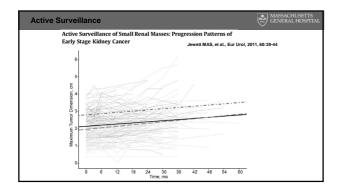


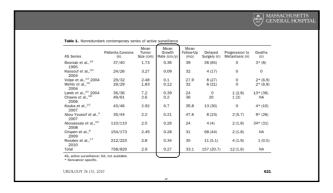


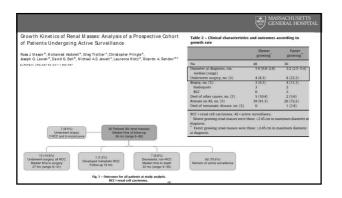


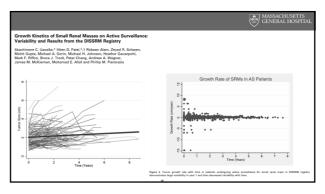


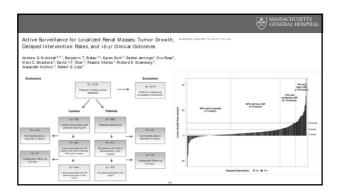


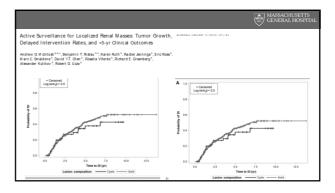


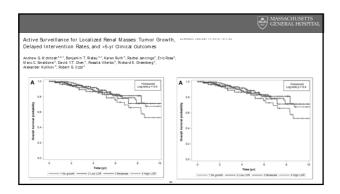


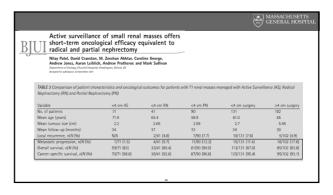


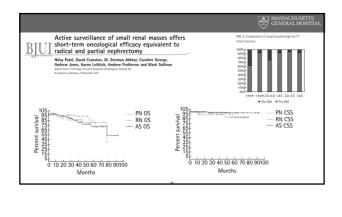


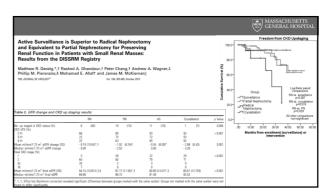


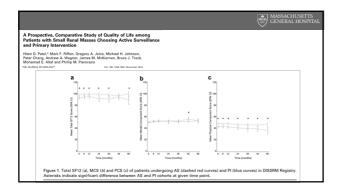


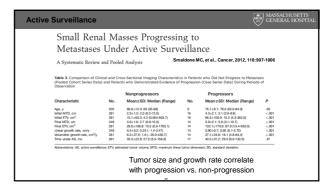


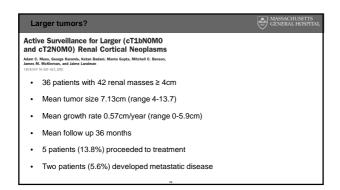


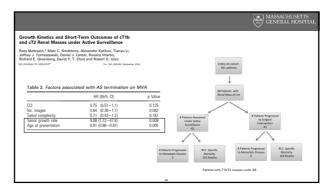


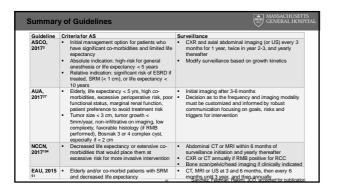


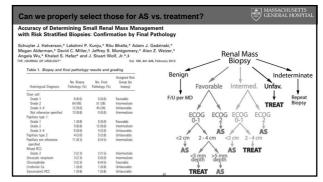


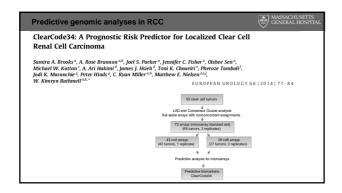


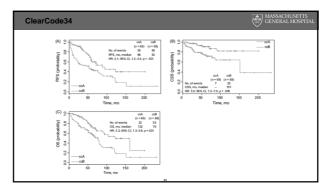


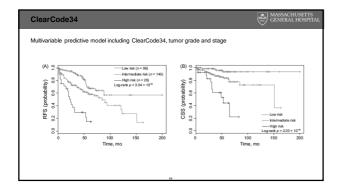


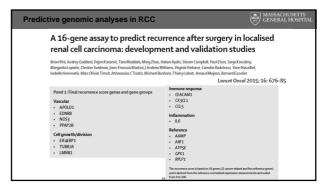


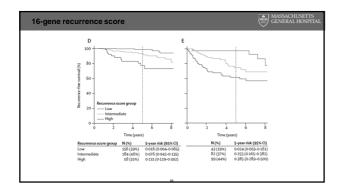


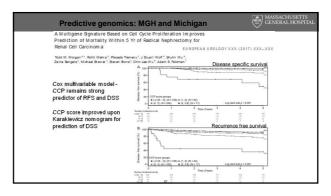


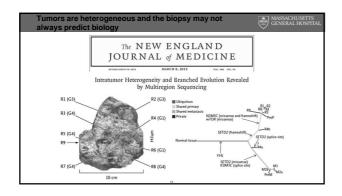


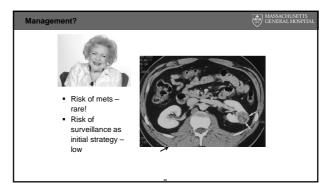


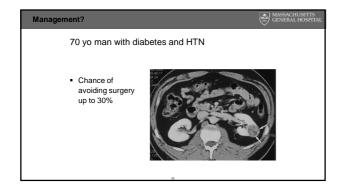


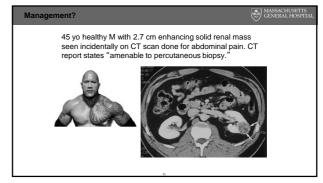












Active Surveillance is an accepted management strategy for small renal masses in appropriately selected patients at greater surgical risk Patients should be monitored carefully for change over time and growth rate, and should be transitioned to treatment if needed Future biomarker and imaging development will hopefully improve our selection of patients for active surveillance



#### Kidney Cancer: Open Surgical Management

#### **MDAnderson** Cancer Center

Making Cancer History

Christopher G. Wood, M. D., FACS Douglas E. Johnson, M. D. Endowed Professorship in Urology Professor and Deputy Chairman, Department of Urology The University of Texas MD Anderson Cancer Center

#### **Disclosures**

- Research Grants: Argos Therapeutics, Pfizer, Bristol Myers Squibb
- · Advisory Role: Merck
- Board Membership: Kidney Cancer Association
- Honoraria: Merck, Argos Therapeutics

#### Open Surgical Management in Kidney Cancer

- There are no absolute indications for open surgical management in Kidney Cancer
- Anything done through open surgical approaches has been replicated laparoscopically or with robotic assisted laparoscopy

   Whether that is good or bad is in the eye of the beholder.....
- · Relative Indications for Open Surgery

  - Venous involvement
     Adjacent organ involvement
     Need for a meticulous and thorough lymph node dissection

  - Complex partial nephrectomies with multiple tumors or complex reconstruction

#### Open Surgical Management in Kidney Cancer

- $\bullet$  The most important tenet of oncologic surgery is oncologic control
- Approach is secondary at most to that tenet
- Having a minimally invasive, cosmetically appealing surgery and not be cured of your cancer serves no one.
- Don't apologize for having open surgery in your repertoire.
  - Choose the approach that most assures it will control the cancer, preserve and maximize renal function, and minimize morbidity to the patient
  - I worry that open surgical techniques may become a "lost art".
  - It is important that we carry ourselves as physicians and surgeons, not technicians.

#### **Incisions**

- Midline
- Flank
  - 11th rib
  - No resection of the rib
- Modified Makuuchi · Adjacent organ invasion
- Large upper pole tumors
- Chevron
- Subcostal

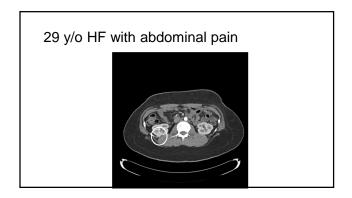


The Role of Lymph Node Dissection in the Management of Renal Cell Carcinoma

#### Relevant Clinical Questions Regarding Lymph Node Dissection for Renal Cell Carcinoma

- $\bullet$  Who should have one? (or when can it be avoided?)

  - Tumor size
     Stage
     Histology
     Lymph node size on imaging or intraoperative assessment
- What is an adequate lymph node dissection?
   Hilar
   Clear off ipsilateral vessel (from hilum?, crus? to bifurcation)
   Is full bilateral
   Full bilateral
- Can an adequate lymph node dissection be performed minimally invasively? (laparoscopic or robotic assisted)



#### Can we all agree that this patient is unlikely to benefit from LND?

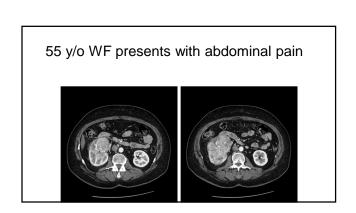
- Arguably may not even need immediate treatment for primary tumor
- Biopsy may guide further therapy
- Potential Exceptions

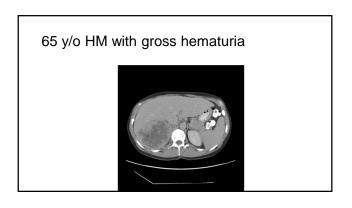
  - HLRCC
     Papillary type II
  - Xp11 Translocation

## 57 y/o WM with gross hematuria

Can we all agree that we would be likely to perform an aggressive LND in the absence of metastatic disease?

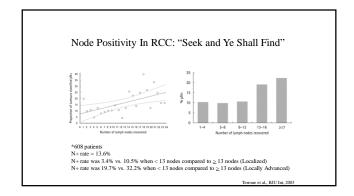
- Benefit unclear
- Evidence level 3 at best
- Role of neoadjuvant/adjuvant therapy unknown
- Knowledge of histology may play a role
- Best chance at "cure" if cure is possible

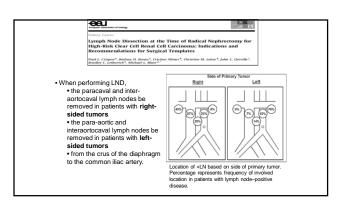


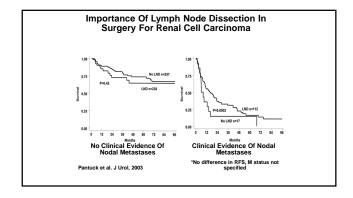


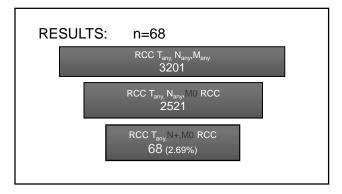
#### Will these patients benefit from LND?

- "Level 1 evidence" says no
- Technique of resection may remove ipsilateral nodes as "collateral damage"
- Staging may be relevant in predicting prognosis and stratification for adjuvant trials
- Clinically relevant question is "Will these patients likely fail regionally, distantly, or both?"









T<sub>any, p</sub>N+,M0 RCC

- Upfront Surgical Therapy:
  - 45% Disease Free at 12 months
  - 22% Long Term Disease Free Status
    - Median Follow Up 43.5 Months
- Papillary Histology
- pN1 v N2 (AJCC v6.0 2002)
- Sarcomatoid Features
- ECOG PS

Delacroix et al., J Urol, 2011

### EORTC 30881: Lymph Node Dissection in Localized RCC

	Without lymph-node dissection (n=389)	With complete lymph-node dissection (n=383)	Hazard ratio	95% confidence interval	p value
Death	135 (35%)	137 (36%)	1.02	0.80-1.29	0.87
Local regional progression	34 (9%)	26 (7%)	0.77	0.46-1.28	0.31
Distant progression	58 (15%)	60 (16%)	1.05	0.73-1.50	0.81
Local or distant progression	93 (24%)	87 (23%)	0.95	0.71-1.27	0.70
Progression or death	156 (40%)	159 (42%)	1.02	0.82-1.28	0.84
Second primary	45 (12%)	36 (9%)	0.79	0.51-1.22	0.28

Blom et al., Eur Urol, 2008

EORTC 30881: Lymph Node Dissection in Localized RCC

			out lymph- dissection	lymp	omplete h-node ection	e	p value
Death	pT category	n	%	n	%	_	0.87
Local region progression		5	1	4	1		0.31
Distant pro	T1	19	5	21	6		0.81
Local or dis progression	T2	230	65	221	63	Ī	0.70
Progression death	Т3	96	27	101	29		0.84
Second prin	T4	2	1	3	1		0.28
	TX	2	1	3	1		

Blom et al., Eur Urol, 2008

Intraoperative Nomogram For Triggering A Lymph Node Dissection: Mayo Clinic

Feature	Odds Ratio (95% CI)	p Value
Nuclear grade:		
1+2	1.0 (reference)	
3 + 4	5.25 (1.99-13.82)	<0.001
Sarcomatoid component	4.11 (2.08-8.12)	<0.001
Tumor 10 cm or greater	2.17 (1.27-3.70)	0.005
Primary tumor stage:		
pT1 + pT2	1.0 (reference)	
pT3 + pT4	2.00 (1.13-3.55)	0.017
Histological tumor necrosis	1.86 (1.00-3.48)	0.051

Blute ML et al., J Urol, 2004

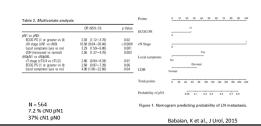
Intraoperative Nomogram For Triggering A Lymph Node Dissection: Mayo Clinic

Proportion of patients with regional lymph node involvement at nephrectomy by number of features in multivariate model

No. Features	No. pN0/pNx (%)	No. pN1/pN2 (%)
Total pts	1,584	68
0	726 (99.6)	3 (0.4)
1	299 (99.0)	3 (1.0)
2	264 (95.7)	12 (4.4)
3	183 (87.6)	26 (12.4)
4	105 (86.8)	16 (13.2)
5	7 (46.7)	8 (53.3)

Blute ML et al., J Urol, 2004

Clinical Predictors of Pathologically Positive Nodes



#### 52 y/o with microscopic hematuria



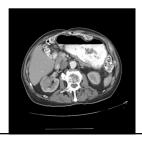
#### Will this patient benefit from LND?

- Likely to be done laparoscopically
- Can an adequate LND be performed laparoscopically and what exactly is "adequate"?
- Arguably, in most cases, a LND will not be done

## 81 y/o undergoing evaluation for possible PE

- No PE found
- Incidental right renal mass
- No evidence of metastatic disease
- s/p open surgery for
  - Deweese clip for DVT
  - Cholecystectomy
  - Partial liver resection for abscess
     Small bowel obstruction with resection

## 81 y/o undergoing evaluation for possible PF



## 81 y/o undergoing evaluation for possible PE

#### DIAGNOSIS

(A) RIGHT KIDNEY:
RENAL CELL CARCINOMA (4.0 CM IN GREATEST DIMENSION),
PAPILLARY TYPE 2, FUHRMAN NUCLEAR GRADE 3, INVASIVE INTO
RENAL PELVIS AND RENAL VEIN. (SEE COMMENT)
Margins of resection (ureteral, vascular and perinephric soft
tissue), no tumor present.

#### Two years later.....



### 81 y/o undergoing evaluation for possible

(C) INTER AORTO/CAVAL, RETROCAVAL, PARACAVAL LYMPH NODES, STUMP OF RENAL ARTERY, STUMP OF RENAL VEIN, URETER: METASTATIC RENAL CELL CARCINOMA, PAPILLARY TYPE, INVOLVING TWO OF TWENTY-EIGHT LYMPH NODES (2/28).

TUMOR MEASURES 3.0 CM IN GREATEST DIMENSION. EXTRANODAL TUMOR EXTENSION PRESENT. Vascular structures consistent with artery and vein and portion of ureter extensively denuded of urothelium with chronic inflammation and focal giant-cell reaction, no tumor present.

#### Is there a benefit to LND?

- This patient would have been saved from a second morbid surgery (older, more medical issues) if he underwent initial LND
- Unclear as to impact on outcome. Currently NED 1 year out

#### 54 y/o presents with pulmonary nodules





#### 54 y/o presents with pulmonary nodules

DIAGNOSIS
(A) RIGHT KIDNEY, ADRENAL, AND PARACAVAL LYMPH NODES: RENAL CELL CARCINOMA (10 X 9 X 4.5 CM) CLEAR CELL TYPE, FUHRMAN NUCLEAR GRADE 4.

WITH MULTIPLE SATELLITE NODULES (RANGING FROM 0.9-2.0 CM). TUMOR INVADES PERINEPHRIC ADIPOSE TISSUE AND ADRENAL GLAND.

TUMOR PRESENT WITHIN MUSCLE CONTAINING VESSELS WITHIN THE RENAL SINUS.

Margins of resection (ureteral, vascular, and peripheral soft tissue), free of tumor.

No lymph nodes identified.

(B) PARACAVAL AND RETROCAVAL LYMPH NODES:

Five lymph nodes, no tumor present (0/5).

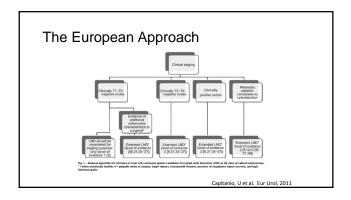
#### 54 y/o presents with pulmonary nodules

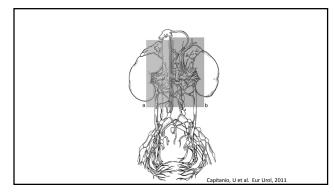




#### 54 y/o presents with pulmonary nodules

- Paracentesis with drain placement: Chylous ascites
- . No fat diet versus TPN with drain
- Systemic therapy delayed indefinitely
- Did not benefit from, and possibly was harmed, by





#### The Role of Lymph Node Dissection in the Management of Renal Cell Carcinoma

- Role of lymph node dissection in locally advanced disease remains undefined
  - Evidence for improved cure rates with LND is lacking
- Improved staging in locally advanced disease is really the only argument to do it, but it implies something can be done to change outcome and that is not necessarily true to date
  - Would still advocate it for more locally advanced disease (where the money is!!!)
- Benefit of LND, with clinically negative nodes, in M1 disease, is completely uncharted waters that needs to be evaluated in the context of a clinical trial.
- Better designed phase III trial(s) are needed to define the role of LND in the appropriate population at risk for nodal disease

Surgical Strategy In Renal Cell Carcinoma With Venous Involvement

#### 50 y/o WM presents with SOB and chest pain





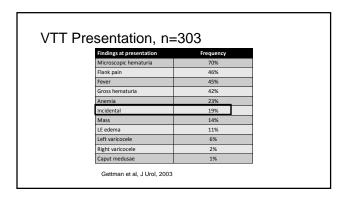
#### Venous Tumor Thrombus (VTT)

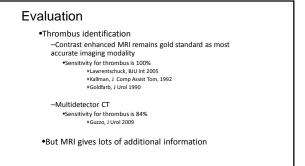
- Most often ccRCC but occurs with all types
- Occurs with non-renal retroperitoneal tumors
  - Urothelial carcinoma
  - Adrenal tumors
  - Wilm's tumor • Metastases to kidneys

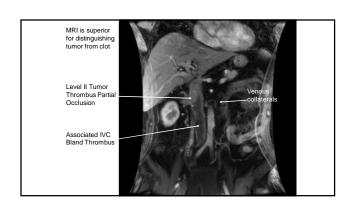




## VTT in RCC Patients •IVC extension 0.5-1.0 Atrial extension







#### **Evaluation**

- Tumor thrombus can progress rapidly
  - Recent imaging is critical for surgical planning
- Staging as for any other advanced renal mass
- Consider anticoagulation
  - IVC occlusion or near occlusion
  - Presence of bland thrombus
- Please NO IVC filter preoperatively

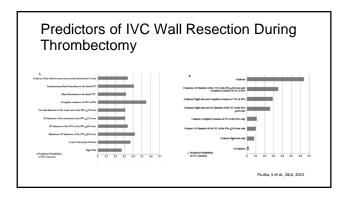
#### Prediction of IVC Wall Invasion

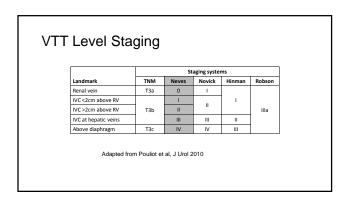
- Zini, J Urol 2008
- Determined that AP diameter of IVC and RV were associated with wall invasion

IVC – 18 mm RV – 14 mm } 90% sensitivity

Mayo data, NCS 2010 RV > 21 mm, IVC > 32 mm assoc w/ wall invasion For each 5 mm increase in diameter there is a 2-fold increased risk of wall invasion

If RV > 27 mm or IVC > 42 mm there was 100% invasion





#### Surgical Technique

- Pre-operative embolization for intracardiac or cavoatrial thrombi
   Decrease intraoperative blood loss?
   Vascularized thrombus regression
   Rarely used anymore
- Midline or Chevron Incision
- Early arterial control key to reducing blood loss
- Ligasure useful for collateralizing vessels
- TEE used intraoperatively to confirm location of thrombus.
   Monitor for evidence of thrombus embolization
- Sternotomy for selected Level III and IV
   Often can do transdiaphragmatic from the abo

#### Surgical Principles for Tumor Thrombectomy

1. Assemble experienced team

•Anesthesia

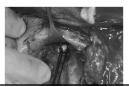
++/- Hepatobiliary, vascular, cardiac surgery

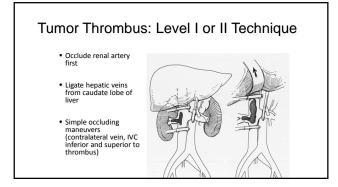
- 2. Operate on vessels first (preserve collateralized veins if IVC occluded)
- 3. Ligate renal artery, no need to embolize
- 4. Isolate venous structures
- 5. Completely remove thrombus
- 6. Manage any distal bland thrombus
- 7. Repair/patch/replace IVC as needed 8. Complete nephrectomy and LND

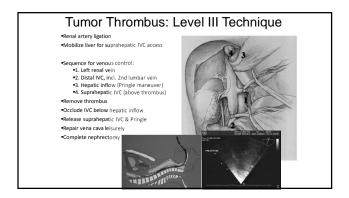
Preoperative Classification	n=160	Tumor Thrombus Presentation	Post Thrombectomy IVC Management	
Group A  IVC – No venous occlusion / No associated distal or bland thrombus	120 (75%)		Cavolomy	
Group B IVC partially occluded / Distal pelvic bland thrombus	4 (2.5%)		Deploy Greenfield Filter	
Group C  IVC total / partial occlusion Associated bland thrombus/	23 (14.4%)		IVC staple ligation	
Group D IVC total occlusion Associated bland thrombus Blute et al, J Urol 200	13 (8.1%)		IVC segmental resection	

#### Avoid Preoperative Embolization

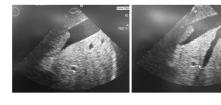
- Subramanian, Urology 2009
- IVC VTT cases 135 with, 90 without embolization
- Embolization associated with increased blood loss, increased complications, increased mortality
- MVA revealed 5 fold increased risk of perioperative death in patients with embolization







#### Intraoperative Ultrasound or TEE



## Tumor Thrombus: Level IV Technique

- Veno-veno bypass
- Cardiopulmonary bypass
- Cardiopulmonary bypass with hypothermic (16°C) circulatory arrest
  - Advantages: bloodless field, ~60 minutes of ischemia time
- Shuch et al, BJUI 2011
- Hypothermic arrest is associated with longer OS and significant reduction in perioperative mortality

#### Presence of Pulmonary Emboli

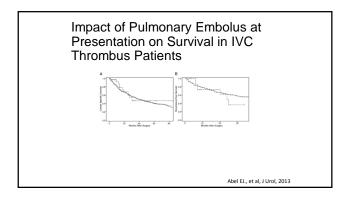


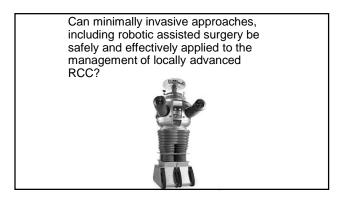


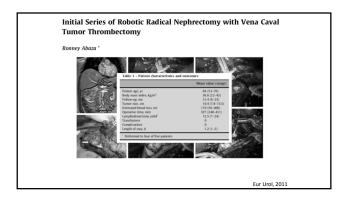
#### Tumor Thrombus Embolism

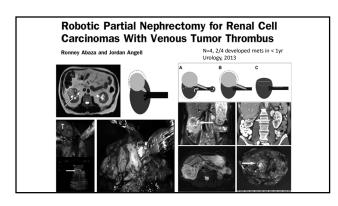
- Kayalar et al, J Thoracic CV surg, 2010
- Reviewed 9 cases of simultaneous RN, RPLND, IVC thrombectomy, and pulmonary embolectomy (7 bilateral, 2 unilateral)
- CP bypass in all 9, hypothermic arrest in 4
- 4 patients received adjuvant therapy
  - 2 patients alive at 4 and 56 months
  - 1 patient died of CVA at 62 months
  - 6 patients died of RCC at 6, 9, 12, 17, 25, & 29 months

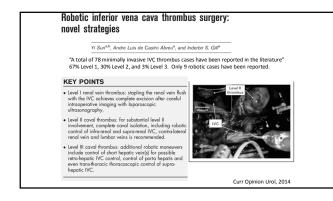












## RCC WITH VENOUS EXTENSION: MDACC 1993-2009 • 605 patients pT3 • Median age 60.5 (28-90) • Follow-up 24.1 months • Median tumor size 10cm, 90% clear cell histology • 45% of patients N0M0 • Level of thrombus • 351 patients - renal vein or smaller branch veins • 208 patients - IVC below diaphragm • 42 patients - IVC above diaphragm

Abel et al., AUA 2011

#### SURGERY FOR RCC WITH VENOUS EXTENSION:MDACC 1993-2009

- Median EBL 900ml and operative time 186 min
- Hospital stay median 6 days
- Complications:

  - 25.4% first 30 days
     9.8% >30 days within 1st year
  - 58% transfusion rate
  - 2.6% 30 day mortality
- Overall survival

  - 66 months for N0M0 patients
     15 months for patients with nodal/ distant metastases

Characteristic		No (%)	
Thrombus level	I	91 (34.3)	
	П	114 (43)	
	III	19 (6.8)	
	IV	41 (15.8)	
M stage		120 (45.3)	
N stage		46 (17.4)	
N + M		31 (11.7)	
Embolization		50 (18.9)	

#### ALL COMPLICATIONS Odds ratio(p-value) MULTIVARIATE Variable UNIVARIATE 3.08 (0.01) 2.14 (0.329) ТЗс N+ HTN 0.89 (0.726) 1.38 (0.21) 0.74 (0.344) CAD 1.26 (0.598) M+ 0.85 (0.544) M+N+ Pringle 0.82 (0.62) 3.23 (<0.001) 1.62 (0.336) CP Bypass 6.22 (0.015) Age≥60 2.53 (0.007) Embolization 2.86 (0.008) 3.63 (0.283) 2.26 (0.025)

MAJOR	COMPLICATION	NS	
Variable	UNIVARIATE	dds ratio(p-value) MULTIVARIATE	
T3c	6.43 (<0.001)	4.23 (0.078)	
N+	0.97 (0.929)		
HTN	1.05 (0.873)	-	
DM	0.44 (0.059)	-	
CAD	1.34 (0.55)	-	
M+	0.89 (0.7)		
M+N+	0.87 (0.766)	-	
Pringle	5.84 (<0.001)	2.78 (0.098)	
CP Bypass	10.71 (0.002)	5.26 (0.198)	
Age≥60	3.52 (0.004)	3.43 (0.022)	
Embolization	2.97 (0.013)	4.4 (0.011)	

MINOR	COMPLICATI	IONS
		Odds ratio(p-value)
Variable	UNIVARIATE	MULTIVARIATE
T3c	1.1 (0.851)	-
N+	0.94 (0.871)	-
HTN	1.13 (0.66)	-
DM	0.54 (0.086)	-
CAD	0.71 (0.496)	-
M+	0.75 (0.315)	-
M+N+	0.83 (0.675)	-
Pringle	2.28 (0.017)	1.22 (0.714)
CP Bypass	3.6 (0.111)	3.31 (0.325)
Age≥60	1.88 (0.091)	1.82 (0.124)
Embolization	2.78 (0.015)	3.01 (0.024)

MORTA	LITY
• Me • Early (< 3 • Pr • Late (30 c	ative 1 vel IV thrombus etastases

## PREDICTORS OF OVERALL SURVIVAL: UNIVARIABLE AND MULTIVARIABLE ANALYSIS • Variables evaluated:

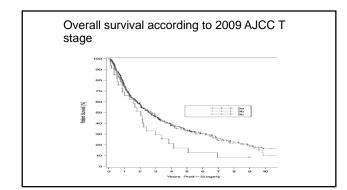
- - age

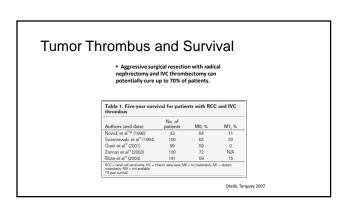
  - gender
     side of tumor · ECOG performance status
  - pathologic features (tumor size, subtype, grade, sarcomatoid features, necrosis, peri-nephric fat invasion, hilar fat invasion, adrenal invasion, positive vein margins, positive surgical margins)
  - Iymph node metastasis
     distant metastasis

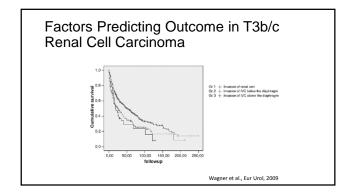
- symptoms at presentation
   time period when surgery was performed
- 2009 AJCC T stage.

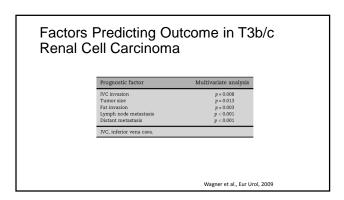
#### Independent predictors of survival

- Clear cell subtype HR 0.55 (CI 0.4-0.8)
- Fuhrman grade IV 1.38 (CI 1.1-1.8)
- Sarcomatoid de-differentiation 1.58 (1.1-2.2)
- Peri- nephric fat invasion 1.50 (1.2-1.9)
- Lymph node metastasis 1.92 (1.5-2.5)
- Distant metastasis 2.30 (1.8-3.0)





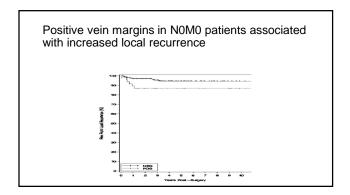


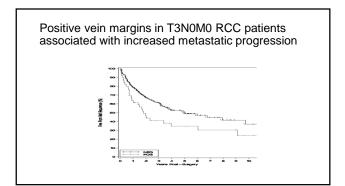


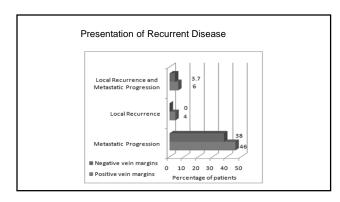
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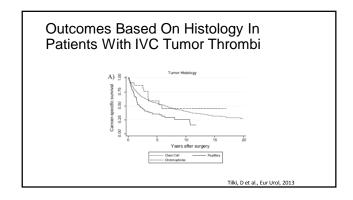
MICROSCOPIC POSITIVE VEIN MARGINS IN T3NOM0 PATIENTS ASSOCIATED WITH INCREASED LOCAL RECURRENCE AND METASTATIC PROGRESSION

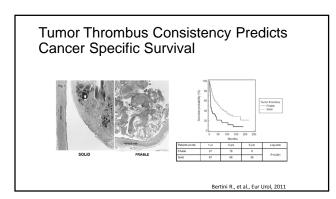
- 270 T3N0M0 RCC patients undergoing surgery
- 19% of patients had cancer present at venous margin of resection
- Positive margins were more likely in patients with higher level thrombus (p<0.001) but no increased risk was detected based on Fuhrman grade (p=0.28).

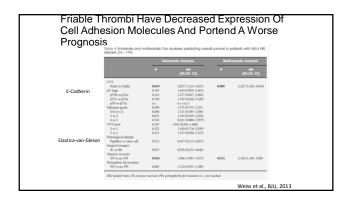


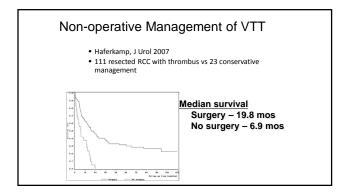


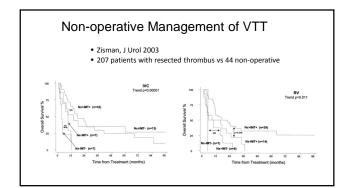




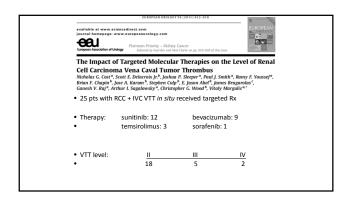




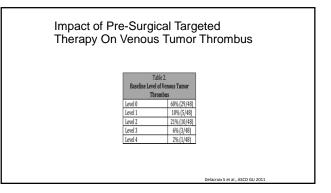


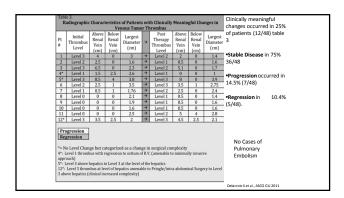


# Targeted Therapy for Tumor Thrombus Multiple case reports of dramatic VTT reduction Di Silverio, Urol Int 2008 Converted IVC thrombus to RV thrombus with 6 months sorafenib Shuch, BJU Int 2008 Conversion of level II to level I thrombus with 4 cycles of sunitinib Karakiewicz, Eur Urol 2008 Converted level IV to level I with 2 cycles sunitinib



	Level	Diameter
Increased	1	8
Stable	21	2
Decreased	3*	11
1 each Level IV-	III, level III-II, level I	I-0
egression limite	d to sunitinib treat	ed patients





# Systemic Therapy in VTT Cases

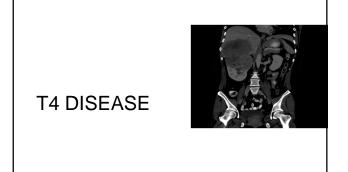
- If no evidence of metastases preferred option is surgical resection reserving systemic therapy for patients that are not surgical candidates
- In patients with metastatic disease performance status and relative burden of disease determine preop vs. post op vs. systemic therapy alone

# BUDD-CHIARI SYNDROME Hepatic Venous Outflow Occlusion • Abdominal pain • Ascites • Hepatomegaly • LE edema • Abnormal LFT's

# BUDD-CHIARI SYNDROME MDACC APPROACH Angioembolization → Interval resection

# Summary

- Radical nephrectomy with IVC thrombectomy is a technically demanding surgery that can be associated with significant morbidity and mortality
- In the absence of metastases, nodal disease, sarcomatoid dedifferentation, and invasion into the perinephric fat or vein wall appear to predict prognosis
- Minimally invasive approaches are described but patient selection appears critical
- Pre-surgical treatment with either embolization or targeted agents does not appear to be helpful and in fact may worsen prognosis

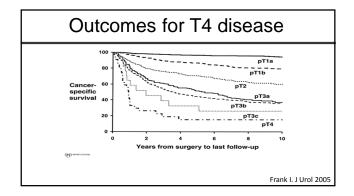


# T4 Renal Cell Carcinoma

- Tumor invades beyond Gerota's fascia
  - Including contiguous extension into the ipsilateral adrenal gland
- Stage IV disease

AJCC Staging, 7th Edition, 2010

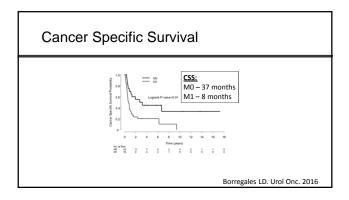
Margulis V. Cancer. 2007

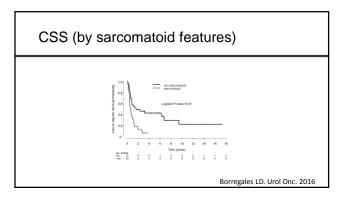


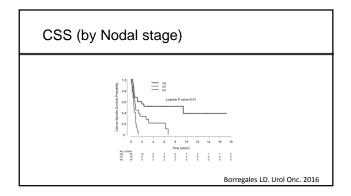
# Clinical T4 Disease • 30 patients with cT4 • All underwent surgery • Only 12 (40%) were pT4 • 18 (60%) were overstaged

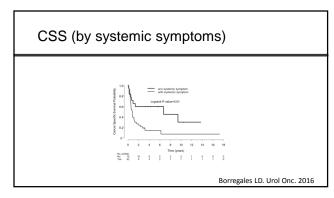
Baseline (	Characteristic	s	
1992 to 2002	Variable	N (%)	
61 patients pT4	Local symptoms		
or patients pri	Yes	36 (59)	
	No	25 (41)	
	Systemic symptoms		
	Yes	42 (68.9)	
	No	19 (31.1)	
	Clinical (Preoperative) T stage		
	<t4< td=""><td>19 (31.1)</td><td></td></t4<>	19 (31.1)	
	T4	42 (68.9)	
	Clinical (Preoperative) N stage		
	N0	29 (47.5)	
	N1	32(52.5)	
	Clinical (Preoperative) M		
	stage	22 (36.1)	
	MO	39 (63.9)	Borregales LD. Urol Onc. 2016
	M1		Borreguies ED. Oror Oric. 2010

Patholog	y Characteristic	s	
	Variable	N (%)	
	Tumor diameter at nephrectomy, cm	13 (10 - 16)	
	Pathological N Stage N0	26 (42.6)	
	N1 Histology	16 (26.2)	
	Clear Cell	47 (77.0)	
	Non-Clear Cell Fuhrman grade	14 (23.0)	
	3 4	14 (25) 39 (69.6)	
	Sarcomatoid dedifferentiation	, ,	
	Yes No	24 (39.3) 37 (60.7)	
		Вс	rregales LD. Urol Onc. 2016









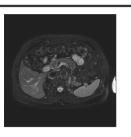
Multivariate Analysis (using only <u>Pre-opera</u>	for CSS <u>ative</u> Varia	ables	)
Variables	Multivaria	te	
	HR (95% CI)	P Value	
Clinical N stage at diagnosis (N1 versus N0)	0.63 (0.33 – 1.22)	0.17	
M stage at diagnosis (M1 versus M0)	1.77 (0.81 – 3.85)	0.15	
Abnormal LDH (Yes versus No)	3.97 (1.87 – 8.43)	<0.01	
Abnormal Alkaline Phosphatase (Yes versus	2.92 (1.47 – 5.80)	<0.01	
No)	Born	egales LC	. Urol Onc. 2016

Multivariate Analysis for ( using only <i>Post-operativ</i>		s)
Variables	Multivariat	e
	HR (95% CI)	P Value
Sarcomatoid dedifferentiation (Yes versus No)	3.11 (1.51- 6.42)	<0.01
Pathological N Stage		
pN1 versus pN0	5.16 (1.94 - 13.69)	<0.01
pNx versus pN0	2.58 (1.15 – 5.79)	0.02
M stage (M1 versus M0)	2.24 (1.01 – 4.98)	0.05
Abnormal LDH (Yes versus No)	2.32 (1.04 - 5.17)	0.04
Abnormal Alkaline Phosphatase (Yes versus No)	4.29 (2.04 - 9.00)	<0.01

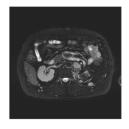
### T4-Take Home Messages

- Survival in patients with pT4 RCC remains poor
  - Median survival of 10 months
- Preoperative identification of patients with pT4 disease is in need of refinement
  - May help improve patient counseling, management, and selection for inclusion in neoadjuvant/presurgical trials

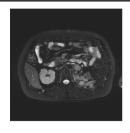
# Local Recurrence after Radical Nephrectomy



# Local Recurrence after Radical Nephrectomy



### Local Recurrence after Radical Nephrectomy



# Local Recurrence after Radical Nephrectomy

• Incidence of <5%

### Local Recurrence: USC

- 11 patients
  - 10 with no metastases at presentation
- Most patients had symptoms
- Presented 31 months after initial surgery
- 2 postoperative deaths
- 2 died of cancer at 8 and 22 months
- 3 died of causes unrelated to cancer recurrence
- 4 patients were without disease at a follow-up of 35, 46, 48 and 211

Esrig D. J Urol. 1992

### Local Recurrence: MDACC

- •16 patients with locally recurrent RCC
  - 8 patients received neoadjuvant Rx, 7 of these received additional adjuvant
    - 7 IFNα based
    - 1 IL-2 based
  - Neoadjuvant group 50% no evidence of cancer
  - Surgery alone group 25% no evidence of cancer

Tanguay S. J Urol. 1996

Itano NB. J Urol. 2000

### Local Recurrence: MDACC

- 15 patients had complete resection (of the 16)
  - 12 had clear margins → 6 were free of cancer
- 12 of the 16 were alive at 2 years after second surgery

Tanguay S. J Urol. 1996

# Local Recurrence: Mayo Clinic Tx including surgery (n=10) Tx excluding surgery (n=11) Tx excluding surgery (n=11) Tx excluding surgery (n=10) Ty excluding s

# Local Recurrence: MD Anderson Experience

- 1990-2014
- 102 patients had surgery for local recurrence
- ullet 84.3% of the patients ullet radical nephrectomy at outside institutions
- → subsequently referred to MDACC for local recurrence surgery

Thomas AZ. J Urol. 2015

# Local Recurrence: MD Anderson Experience

- Time from nephrectomy to local recurrence diagnosis was 1.5 years
- At time of nephrectomy
  - Median age 55 years
  - 79.4% had open surgery
  - 60.8% were pT3-4 (invading renal vein/vena cava, fat or other organs)
  - 19.6% were pN1 (positive lymph nodes)
  - 13.7% had positive margins

Thomas AZ. J Urol. 2015

# Local Recurrence: MD Anderson Experience

- Area of local recurrence
  - 48% Soft tissue/renal fossa
  - 40.2% Lymph nodes11.8% Adrenal gland
- At time of local recurrence surgery
  - 41.2% had symptoms
  - 45.1% received neoadjuvant Rx

Thomas AZ. J Urol. 2015

### Local Recurrence: MD Anderson Experience

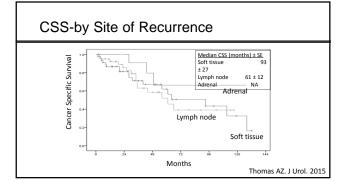
- Median local recurrence size = 4.5cm
- Open surgery for 97.1% of patients
- Major complications = 14.7%
- Blood loss = 700 mL
- Median surgery duration = 3.5 hours
- Median hospital stay = 1 week

Thomas AZ. J Urol. 2015

# Local Recurrence: MD Anderson Experience

- 58.8% of patients had cancer relapse after local recurrence surgery
  - Median time to second relapse ~ 2 years
  - Median survival after second relapse ~5.5 years
- Predictors of worse outcomes after surgery for local recurrence
  - · Positive lymph nodes at time of initial nephrectomy
  - Larger size of local recurrence

Thomas AZ. J Urol. 2015



# Resection of Isolated Retroperitoneal LN Recurrence

- 50 patients, 4 tertiary centers
- $\bullet$  Median (IQR) time to RPLN recurrence after nephrectomy  $\Rightarrow$ 12.6 (6.9-39.5) months
- Median (IQR) follow-up after RPLN resection → 28.0 (13.7-51.2) months
- 26 patients developed RCC recurrence, at a median (IQR) of 9.9 (4.0-18.5) months after RPLN resection

Russell CM. BJU Int. 2016

# Resection of Isolated Retroperitoneal LN Recurrence

- 11 patients subsequently died (10 DOD)
- Median PFS after RPLN resection → 19.5 months • 5-year PFS → 35.4%
- RPLN recurrence at ≤12 months after nephrectomy → with a significantly (p=0.003) inferior median PFS (12.3 months) compared with RPLN recurrence at >12 months after nephrectomy (47.6 months)

Russell CM. BJU Int. 2016

### Resection of Recurrent IVC Thrombus

- 16 patients (1970-2013)
  - 3 synchronous widely metastatic disease → no surgery (DOD <6 mo)
  - 13 → surgery
    - Median time from prior nephrectomy to diagnosis of 6 mo (range: 3-58)
    - Surgical resection was completed in 11 (2 unresectable)- median blood loss 2500 ml (range: 200–7000)
    - Median time to recurrence → 4mo
    - Median time to death > 12 mg
    - All patients recurred and died of disease (median follow-up of 12 mo)

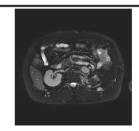
Parker WP. Eur Urol Focus. 2016

# SABR of IVC Thrombus

- 2 cases of level IV thrombus treated with SABR (50Gy, 36Gy)  $\rightarrow$  Alive at 2 years, and at 18 months
- Ongoing prospective trial
  - NCT02473536

Hannan R. Cancer Biol Ther. 2015

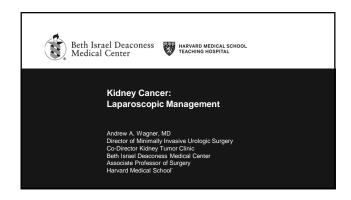
# Local Recurrence after Radical Nephrectomy

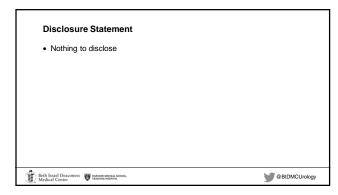


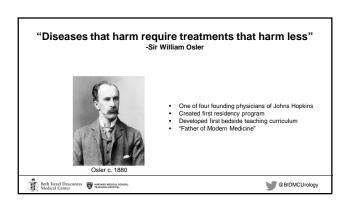
- <u>Treatment</u>
  -Resection of all retroperitoneal masses -Resection of renal artery and vein stump
- -Distal pancreatectomy (Thanks M. Katz!)
- -Left hemicolectomy
- -Left adrenalectomy
- -Omentectomy
- -Partial diaphragm resection
- -RPLND
- → NED 21 months postop

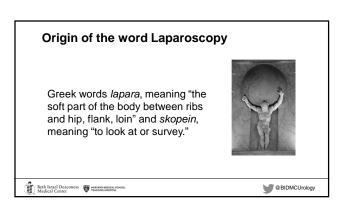
# Take Home Messages

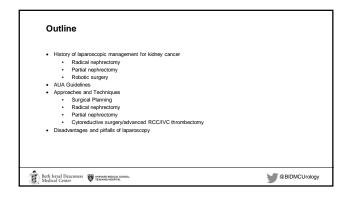
- Local recurrences are rare but can occur after initial treatment
- Important to follow-up with urologist after initial treatment
- Best treated in referral medical centers

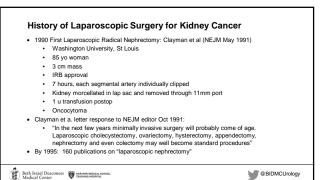






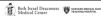












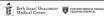


#### History of Laparoscopic Surgery for Kidney Cancer

- Reports of retroperitoneal approach, nephroureterectomy, lap partial nephrectomy, and retroperitoneal PN soon followed
  Hand assisted surgery afforded surgeons without extensive laparoscopic training the ability to perform LN while maintaining the benefits of minimally invasive surgery
- Retroperitoneal surgery remained challenging due to lack of dilating balloons, small working space, difficulty maintaining pneumoperitoneum

  Concerns remained about morcellation and tumor spillage, cancer control, difficult learning
- However early studies demonstrated early recovery and less pain medicine requirements for LRN

  - McDougall et al J Urol 1996: compared 17 LRN to 12 ORN Decreased morphine requirements, time to normal activity, time to full recovery

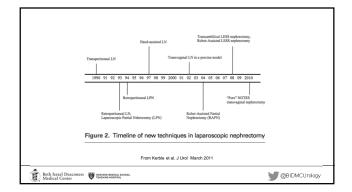


Beth Israel Deaconess W HARVARD MEDICAL SCHOOL Medical Center





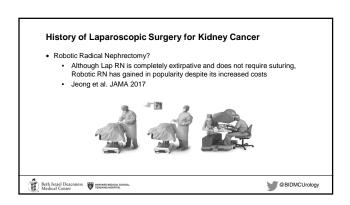
@BIDMCUrology

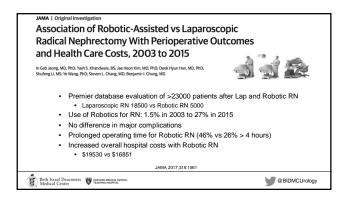


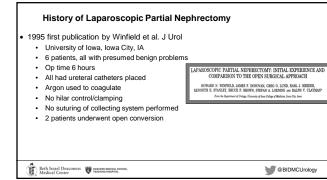
# LAPAROSCOPIC RADICAL NEPHRECTOMY FOR RENAL TUMOR: THE WASHINGTON UNIVERSITY EXPERIENCE ELSPETH M. McDOUGALL,\* RALPH V. CLAYMAN AND OSAMA M. ELASHRY Mcdougall et al J Urol 1996: compared 17 LRN to 12 ORN Op time LRN 6.6 vs ORN 2.3 hrs Hospital stay LRN 4 vs ORN 8 days Decreased morphine requirements, time to normal activity, time to full recovery after LRN Obtaining pneumoperitoneum in lateral position saves time No need for preoperative stent placement Prefer to remove intact specimen High rate of incisional hernias with flank extraction incision compared to lower midline incision Total charges for LRN \$2000 higher than ORN

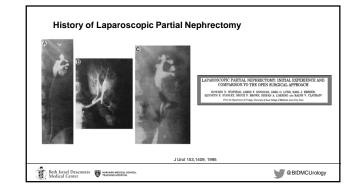
J Urol 1996, 155:1180

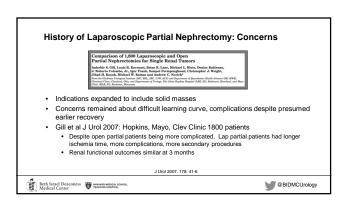
# History of Laparoscopic Surgery for Kidney Cancer · Reports of equivalent cancer control led to increased adoption of LRN · Chan et al J Urol 2001: no difference in disease free survival between LRN and ORN By 2000 55% of cases at Johns Hopkins were performed as LRN (Permpongkosol et al BJU Int 2006) @BIDMCUrology Beth Israel Deaconess HARVARD MEDICAL SCHOOL MEDICAL SCHOOL MEDICAL SCHOOL SCHO

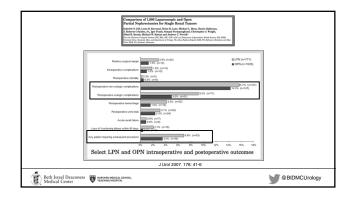


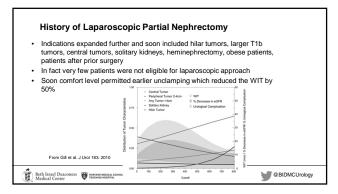


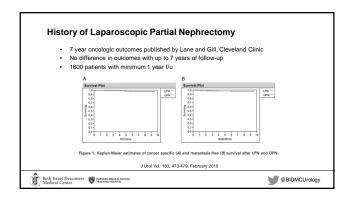


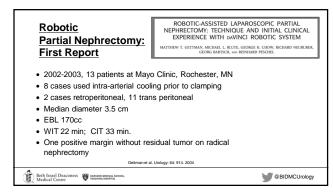


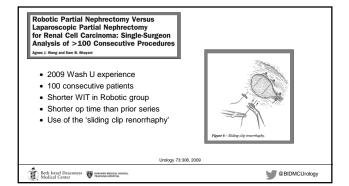


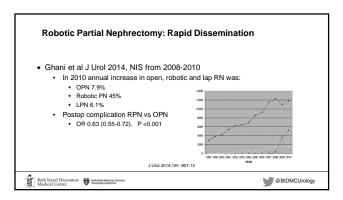


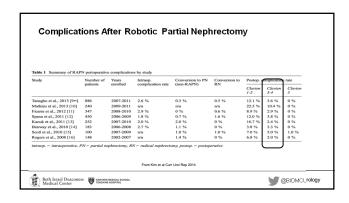


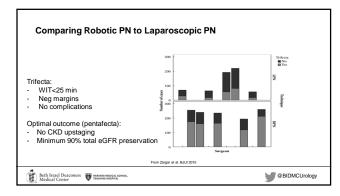






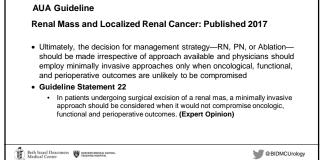


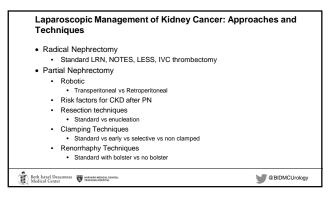


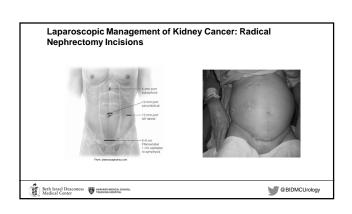


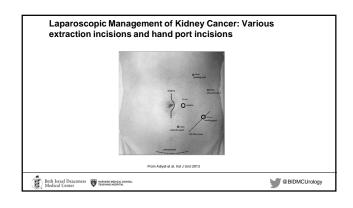
BIDMCUrology

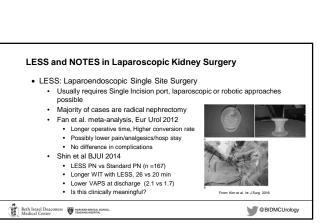
# Comparing Robotic PN to Laparoscopic PN Choi et al Eur Urol 2015 Meta analysis LPN vs RPN • 23 studies, 2240 patients Lower conversions to radical and open surgery Shorter WIT · Less change in eGFR · Shorter LOS Beth Israel Deaconess HARVARD MEDICAL SCHI Medical Center HARVARD MEDICAL SCHI

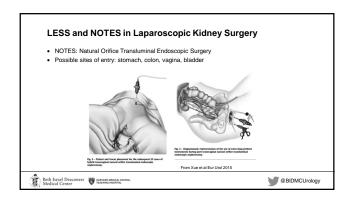


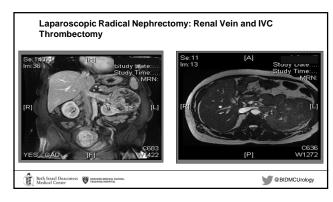


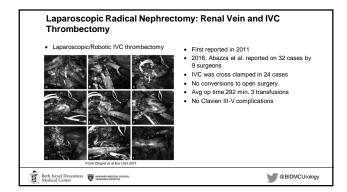


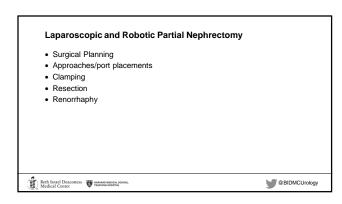


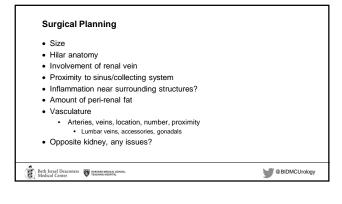


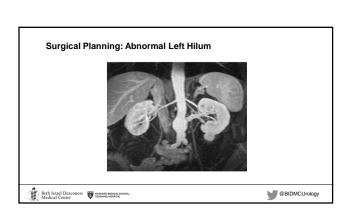


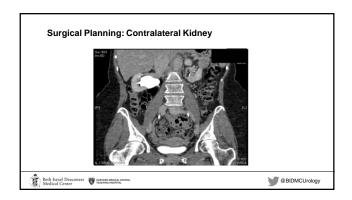


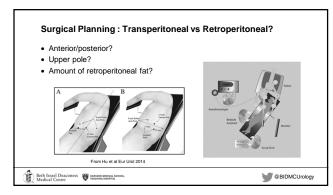


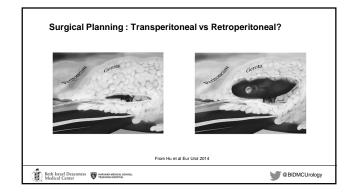


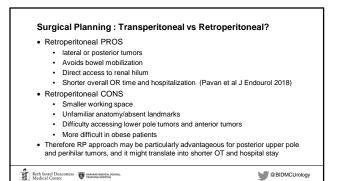


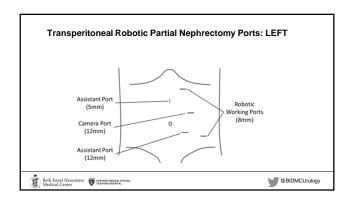


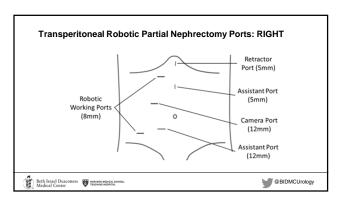


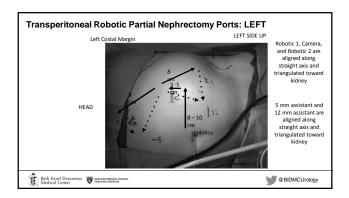


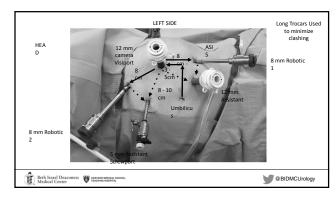


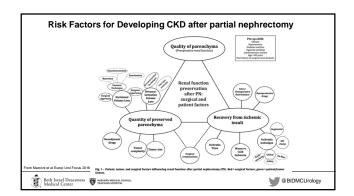


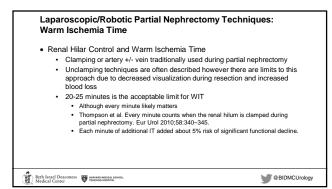


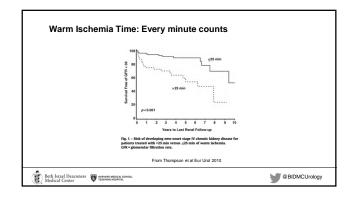


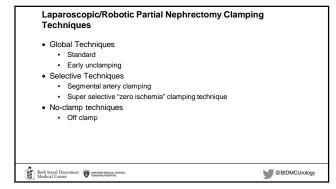


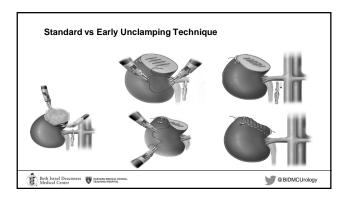






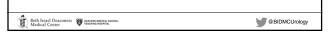


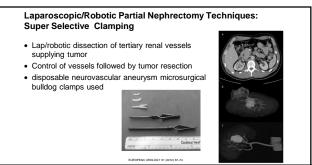




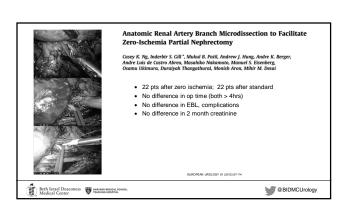
#### Standard vs Early Unclamping Technique (EU)

- EU May be more applicable (than selective clamping) to majority of robotic surgeons as it does not require dissection of tertiary vessels
- WIT is typically <15 min.
- Risk of delayed complications including urine leak and pseudoaneurysm extremely low
  - Of 403 patients after RPN at BIDMC using early unclamping without bolsters or fibrin glue products: one urine leak (in pt with complex pyelolithotomy on IS) and no episodes of delayed bleeding or pseudoaneurysm
  - Likely due to suturing of collecting system and sinuses under direct vision.
     Also direct suturing of arterial bleeders after unclamping.





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Robotic Partial Nephrectomy with Superselective Versus Main Artery Clamping: A Retrospective Comparison

Milit And Deal's Andre Lusis de Custro Ahreis, Sorte Lief, Jet Cal, Eric YI-Hsisi Huang, Pierre-Marie Levandovisk, Demits Lee, Arjum On Ibamararijo, Andre K. Berger, Alvin Goli, Osamu Uklimura, Monish Aron, Inderbit S. Cill

\* Robotic superselective clamping

• 58 superselective PN; 63 standard RPN

• Op time 301 min for superselective; 229 standard

• Superselective tumors larger and more hilar location

• Bolsters used in 41% and 32%

• Transfusion: 24% and 6%

• Superselective: 3 urine leaks, PE

• Standard: 1 urine leak, PE

• Standard: 1 urine leak, PE

• Change in eGFR was -11% and -17% with f/u 4-6 months (p=0.03)

@BIDMCUrology

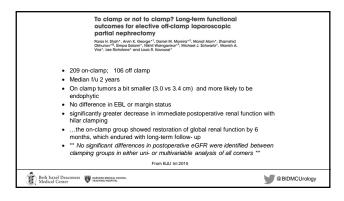
Laparoscopic/Robotic Partial Nephrectomy Techniques:
Zero Ischemia – "OFF Clamp" Partial

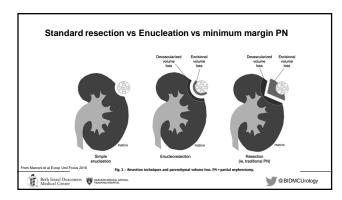
• Lap or Robotic resection without any hilar clamping

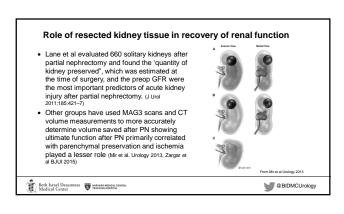
• Very challenging procedure due to ongoing blood loss and poor visualization

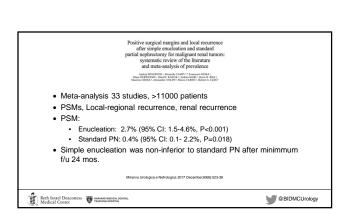
• No ischemia to segmental or entire kidney, thus is there a renal functional benefit?

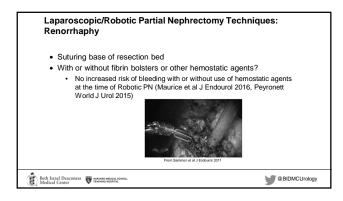
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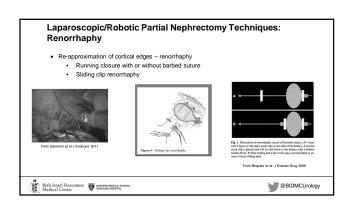












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#### Conclusions

- Vast majority of kidney cancer cancer cases can be approached either laparoscopically or robotically with appropriate training and experience
- Modifiable risk factors for CKD include WIT and amount of kidney parenchyma lost after PN
- Advanced techniques in experienced hands include robotic IVC thrombectomy and super selective clamping for  $\ensuremath{\mathsf{PN}}$
- NOTES and LESS are still exploratory and await improved technology prior to more widespread application
- Hemostatic agents during robotic partial nephrectomy do not reduce bleeding risk





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# Kidney Cancer – Systemic Therapy for Advanced Disease

David McDermott, MD Leader, Kidney Cancer Program Dana-Farber/Harvard Cancer Center

# **Disclosures**

### Consultant

- Array Biopharma
- Bristol-Myers Squibb
- Calithera Biosciences
- Exelixis
- Genentech
- Merck
- Novartis
- Pfizer

#### Research funding

- · Prometheus Labs
  - Bristol-Myers Squibb

2

# Kidney Cancer: Epidemiology

U.S. New cases/deaths\*
% of all cancers/ deaths

63,340/14,970

Male predominance

3:2 ~64

Median age ~64Smoking and obesity are known risk factors

Incidental findings increasing

Stage: local

 local
 60-70%

 regional
 5-10%

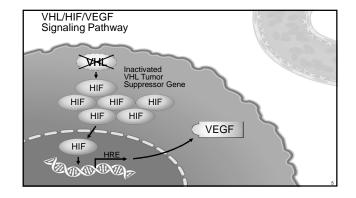
 metastatic
 15-20%

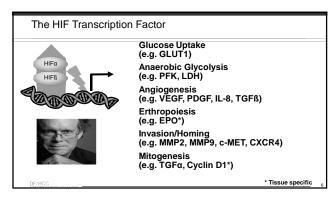
40% will eventually develop Stage IV disease

\*American Cancer Society, 201

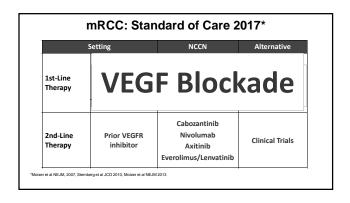
# Where are the best targets in Advanced RCC?

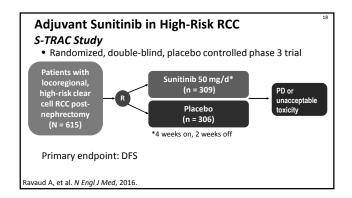
- · One answer: the vHL Pathway
- Why?
  - Tumor suppressor gene
  - Commonly inactivated in clear cell RCC (70%)
  - Inactivation induces hypoxia-regulated genes
  - Promoting angiogenesis and tumor growth

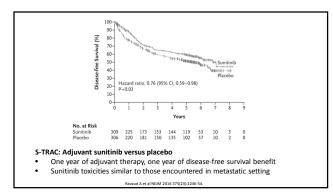


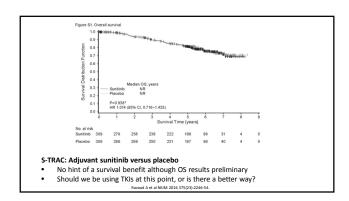


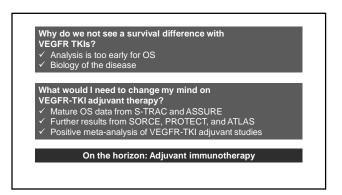
	Setting	NCCN <sup>a</sup>	Alternative	
4-4-15	Good or	Sunitinib Pazopanib	HD IL-2 <sup>b</sup> Axitinib	
1st-Line Therapy	intermediate risk	Bevacizumab + IFNα	Cabozantinib <sup>b,c</sup>	
	Poor risk	Temsirolimus		
2nd-Line Therapy	Prior VEGFR inhibitor	Cabozantinib Nivolumab Axitinib Everolimus/Lenvatinib	Clinical Trials	

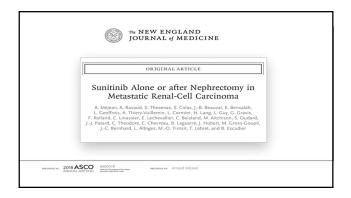


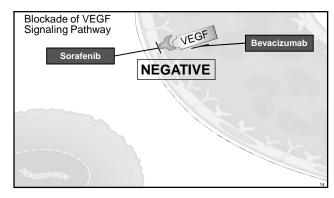


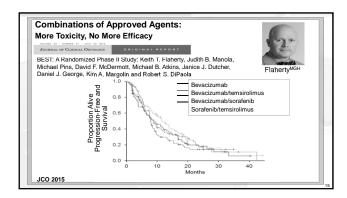


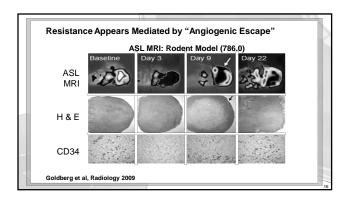


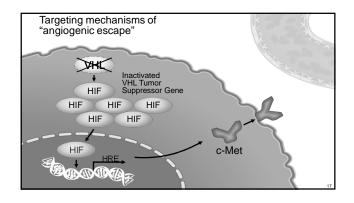


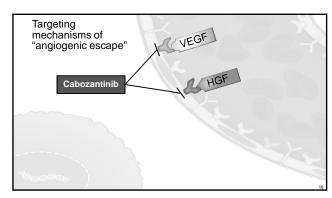


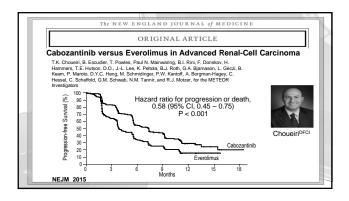


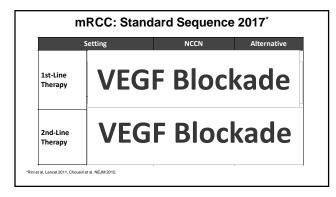


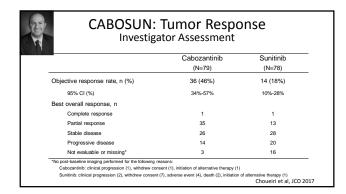


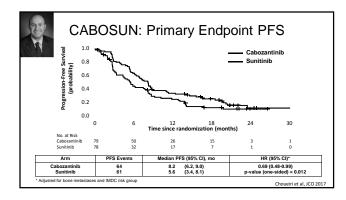


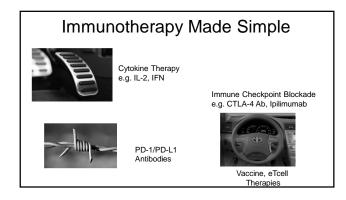


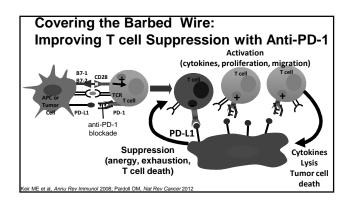


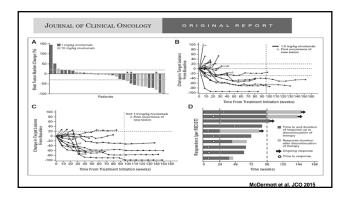


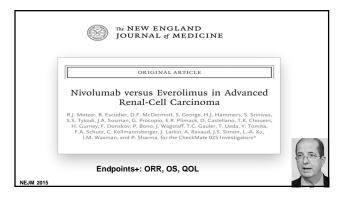


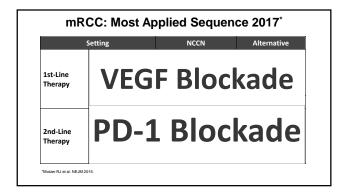


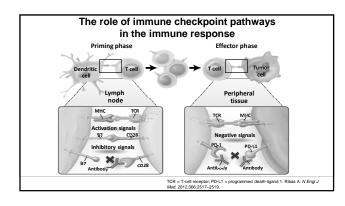


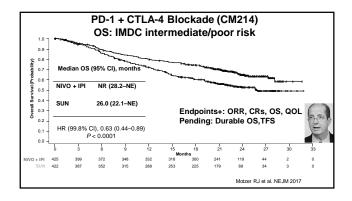


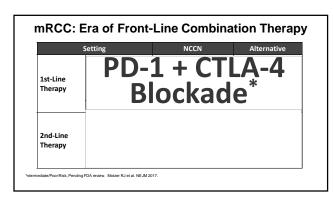


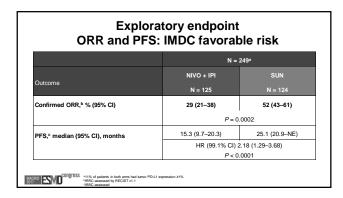


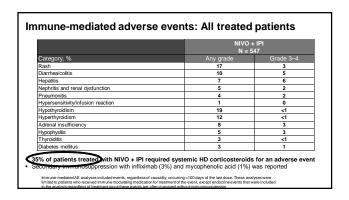


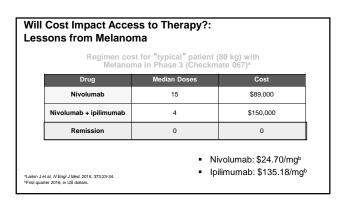


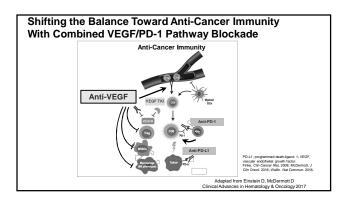


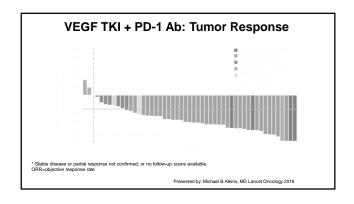


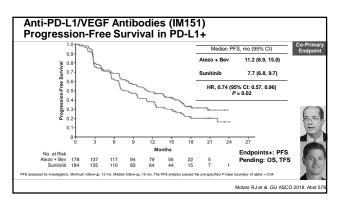


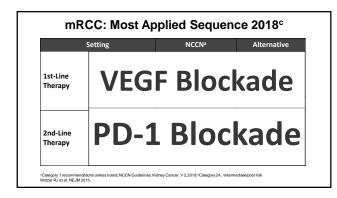


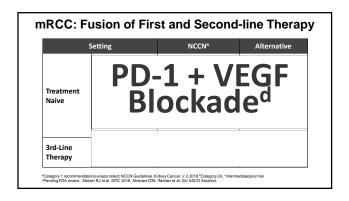


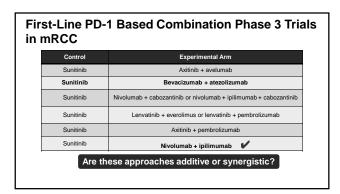


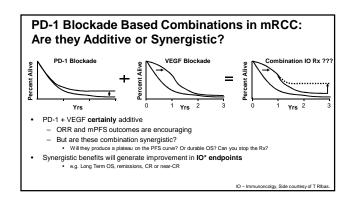


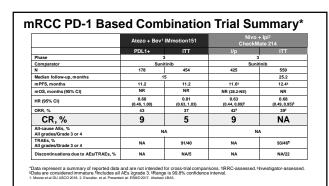


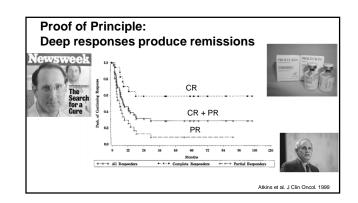


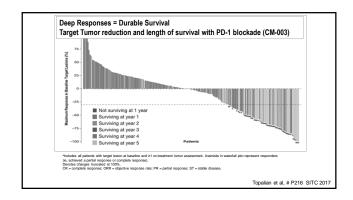


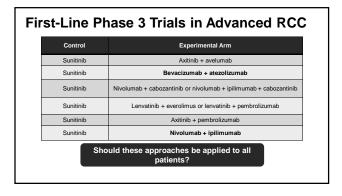












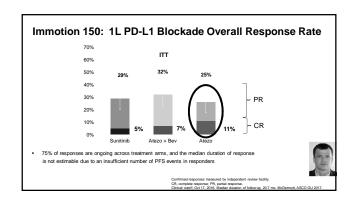


# **First-Line PD-1 Based Combination** Phase 3 Trials in mRCC

- Important Unanswered Questions:
  - Are benefits outweighed by costs?
  - Is combination > sequence?
    - PD-1 + X > VEGF
      But is PD-1 + X > VEGF followed by PD-1?
      - - Not well studied yet
  - What is the activity of PD-1 Blockade in first-line?

	Nivolumab N = 410	Everolimus N = 411
Objective response rate, %	25	5
Odds ratio (95% CI) P value	5.98 (3.6 <0.0	68-9.72) 0001
Best overall response, %		
Complete response	1	1
Partial response	24	5
Stable disease	34	55
Progressive disease	35	28
Not evaluated	6	12
Median time to response, months (range)	3.5 (1.4-24.8)	3.7 (1.5–11.2)
Median duration of response, months (range)	12.0 (0-27.6+)	12.0 (0-22.2+)
Ongoing response, n/N (%)	45/103 (44)	8/22 (36)

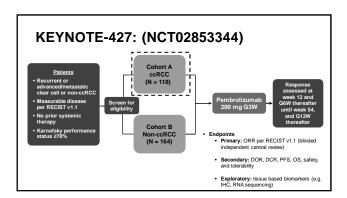
	Setting	NCCN <sup>a</sup>	Alternative
		Sunitinib	
1st-Line Therapy	Nivolu	mab + Ipilir	numab
	Poor risk*	Temsirolimus	Cabozantinib
2nd-Line Therapy	Prior VEGFR inhibitor	Cabozantinib, Nivolumab, Axitinib, Everolimus/ Lenvatinib	Clinical Trials



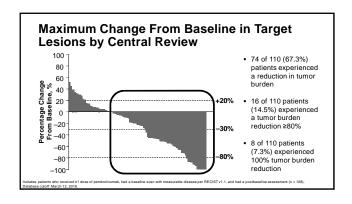
## Pembrolizumab Monotherapy as First-Line Therapy in Advanced Clear Cell Renal Cell Carcinoma: Results From Cohort A of KEYNOTE-427

D. F. McDermott<sup>1</sup>; J-L. Lee<sup>2</sup>; C. Szczylik<sup>2</sup>; F. Donskov<sup>4</sup>; J. Malik<sup>2</sup>; B. Y. Alekseev<sup>5</sup>; J. M. G. Larkin<sup>7</sup>; V. B. Matveev<sup>5</sup>; R. A. Gafanov<sup>5</sup>; P. Tomczak<sup>1</sup>; S. S. Tykodi<sup>1</sup>; P. F. Geertsen<sup>1</sup>2; P. Wiechno<sup>1</sup>5; S. J. Shin<sup>1</sup>4; F. Pouliot<sup>1</sup>5; T. A. Gordoni<sup>6</sup>; W. Li<sup>1</sup>17; R. F. Perlini<sup>1</sup>8; C. Schlossi<sup>1</sup>8; M. B. Atkinsi<sup>18</sup>

These of Section Services Control, Control, Mark Life, Visual Andread Control and University of United College of Macrons, Seed Regular of Known, Wignlaws of Macrons, Seed Regular of Known, Wignlaws of Control Regular of Macrons, Seed Regular of Known, Wignlaws of Mark Life, Seed Regular of Known, Wignlaws of Mark Life, Seed Regular of Known, Wignlaws of Mark Life, Seed Regular of Known, National Control Regular Online of Control



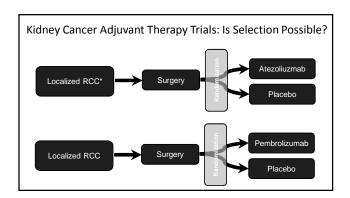
#### Confirmed ORR by Blinded Independent **Central Review** N = 110 % 95% CI ORR 42 38.2 29.1-47.9 DCR (CR + PR + SD ≥6 months) 49.3-68.4 65 59.1 Best overall response 3 2.7 PR 39 35.5 SD 35 31.8 PD 31 28.2 No assessment 1.8



n (%) N = 110	Any Grade (≥5% of pts)	n (%) N = 110	Grade 3/4 (≥2 pts)	
Any	88 (80.0)	Any	24 (21.8)	
Pruritus	30 (27.3)	Diarrhea	4 (3.6)	
Fatigue	27 (24.5)	Colitis	3 (2.7)	
Diarrhea	21 (19.1)	Asthenia	2 (1.8)	
Rash*	17 (15.5)	Hepatitis	2 (1.8)	
Arthralgia	14 (12.7)	AST increased	2 (1.8)	
Hypothyroidism	11 (10.0)	Hyponatremia	2 (1.8)	
ALT increased	8 (7.3)	Hypophosphatemia	2 (1.8)	
AST increased	8 (7.3)			
Asthenia	7 (6.4)	<ul> <li>Discontinuation because was reported in 12 (10.9</li> </ul>	of a treatment-related AE	
Decreased appetite	7 (6.4)	was reported in 12 (10.9	70) patients	
Dry mouth	7 (6.4)	<ul> <li>High dose steroids<sup>b</sup> were</li> </ul>	administered in 14 patien	
Influenzalike illness	6 (5.5)	(12.7%)		

### **Conclusions**

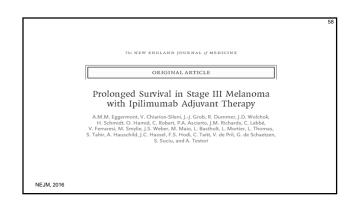
- Pembrolizumab has shown promising antitumor activity as monotherapy in first-line ccRCC across IMDC risk groups, with ORR 38%
  - Encouraging activity was also observed in key subgroups, such as IMDC intermediate/poor risk (ORR, 42%) and patients with PD-L1-positive tumors (ORR, 50%)
  - ORR of 32% in patients with IMDC favorable risk
- Safety profile in KEYNOTE-427 cohort A was similar to the previously described safety profile of pembrolizumab in other tumor types
- Cohort B of KEYNOTE-427, to explore the role of pembrolizumab monotherapy in non-ccRCC patients, is ongoing
- Results presented herein provide support for the exploration of pembrolizumab in the adjuvant setting (KEYNOTE-564 NCT03142334, currently enrolling) and will allow investigators to put the benefit of anti-PD-1-based combination therapies in better context



# Phase 3 Trials Assessing Adjuvant Immunotherapy for High-risk Localized RCC<sup>1</sup>

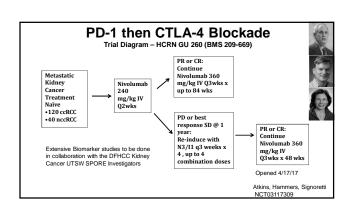
Treatment Arms	Primary Endpoint	Trial	ClinicalTrials.gov ID
Atezolizumab vs Placebo	DFS	IMmotion010	NCT03024996
Pembrolizumab vs Placebo	DFS	KEYNOTE-564	NCT03142334
Neoadjuvant nivolumab → Surgery → adjuvant nivolumab vs observation	RFS	PROSPER RCC	NCT03055013
Nivolumab + ipilimumab vs placebo	DFS	CHECKMATE 914	NCT03138512
Durvalumab vs durvalumab + tremelimumab vs active surveillance	DFS and OS	RAMPART	NCT03288532

1. https://www.clinicaltrials.gov. Assessed May 6, 2018.



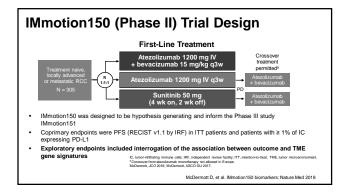
### **Rational Application of Combination IO Therapy:**

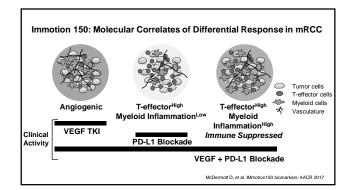
- Trial Design
  - Sequence and Combination Comparisons
    - e.g. PD-1/CTLA-4 vs PD-1/VEGF
  - Flexible Combinations
    - Can you build on single agent PD-1?
    - What happens when you stop rx?
- · Patient Selection
- Novel Endpoints

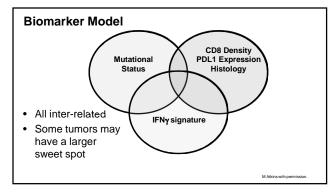


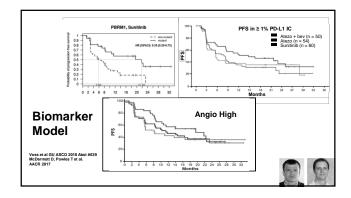
## **Rational Application of Combination IO Therapy:**

- Trial Design
- · Patient Selection
- Novel Endpoints



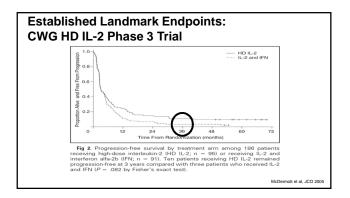




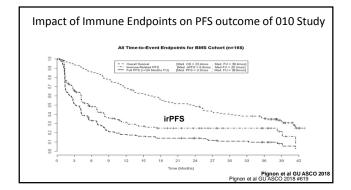


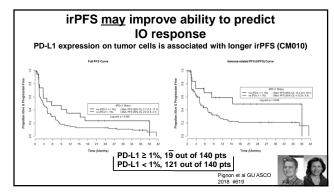
# Rational Application of Combination IO Therapy:

- Trial Design
- · Patient Selection
- Novel Endpoints
  - Make IO Endpoints Primary
    - Speed R&D
    - · Achieve patient's goal



# The Future of Immunotherapy • Combination therapy based on pre-clinical models - Freeman<sup>DFC</sup>/Sharpe<sup>IMS</sup> PIs - NeoVax - Choueiri/Wu<sup>DFCI</sup> PIs • Front-line/Adjuvant therapy - PROSPER (Nivo) - Harshman<sup>DFCI</sup> PI - Atezo - Pal<sup>COH</sup>, Uzzo<sup>FCCC</sup> - PIs - Pembro - Choueiri<sup>DFCI</sup> - PI • Predictive biomarker development

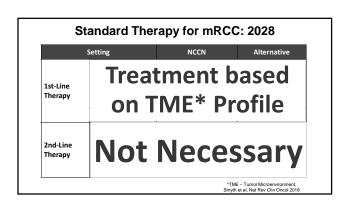




# **Conclusions**

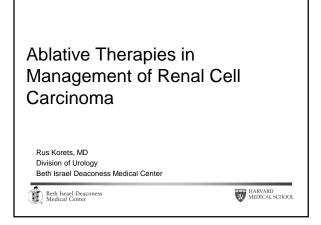
Rational application of sequential Rx in RCC:

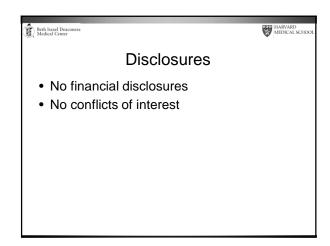
- FDA Support for:
  - Innovative Trial Design
  - IO Endpoints
  - Next Gen Biomarkers
- Focus on the Patient's Goal:
  - Increasing Treatment-free Survival

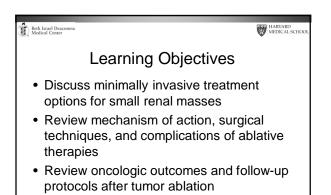


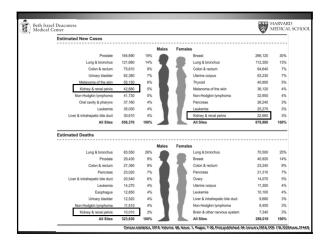
# Acknowledgements

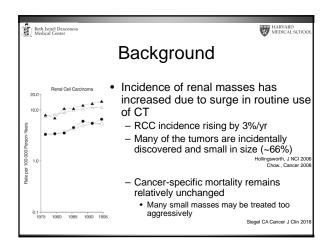
- Participating study investigators and clinical sites
- The Immotion 150/151 studies were sponsored by F. Hoffmann-La Roche, Ltd, Checkmate 214 by Bristol-Myers Squibb, Keynote 427 by Merck
- Genentech Translational Team
  - Mahrukh Huseni, Priti Hegde
- DF/HCC KCP SPORE Colleagues

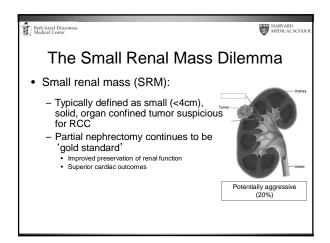


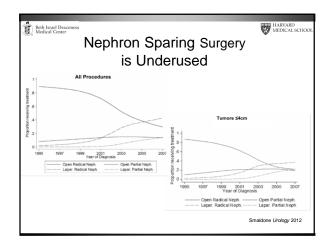


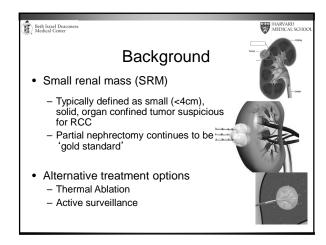


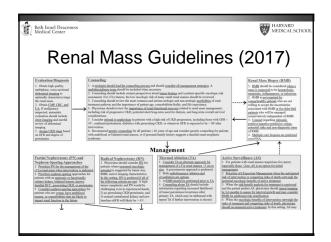


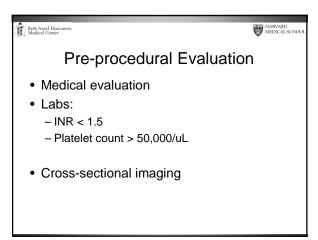


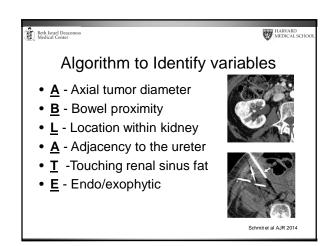


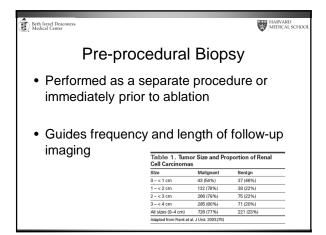


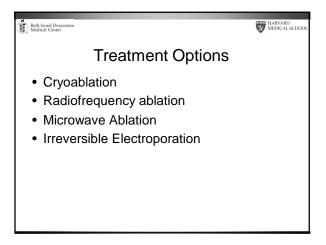


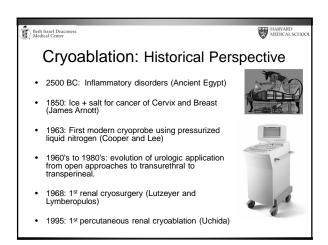


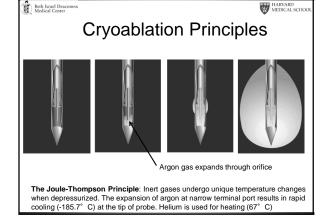


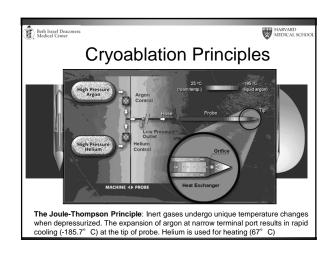


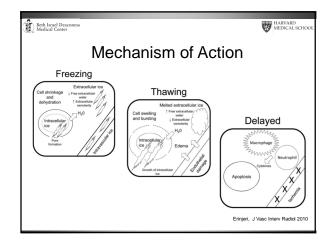


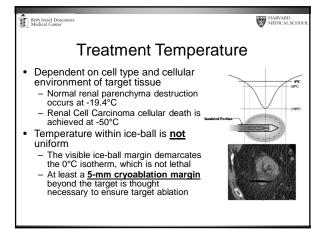


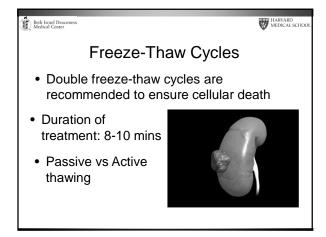


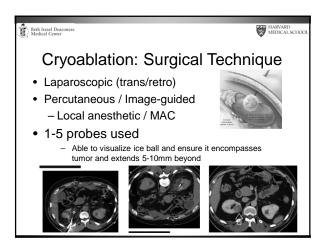


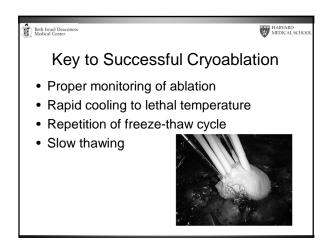


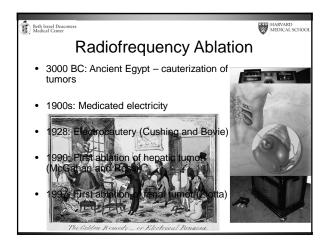


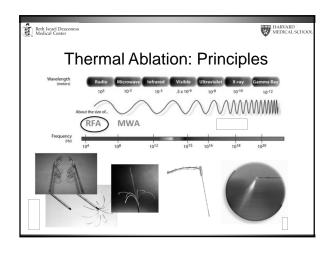


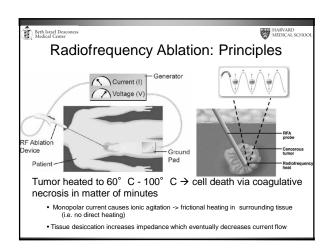


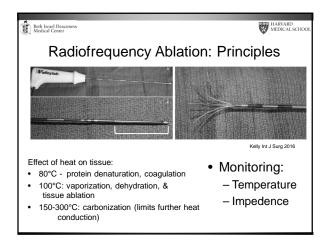


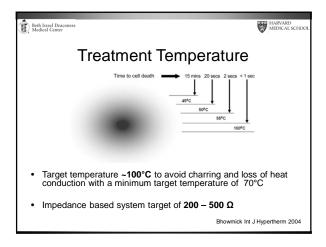


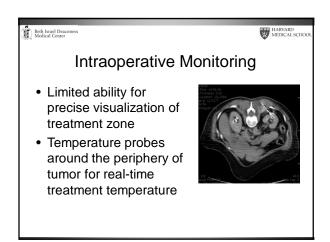


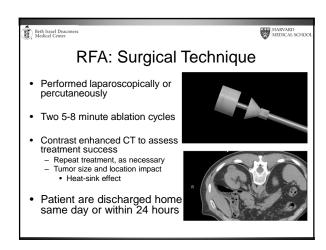


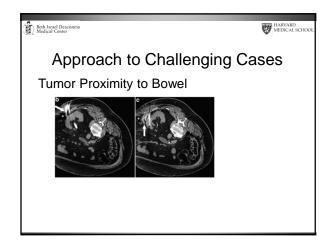


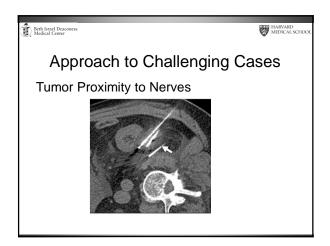


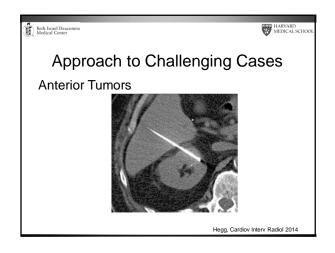


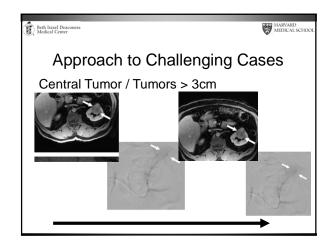


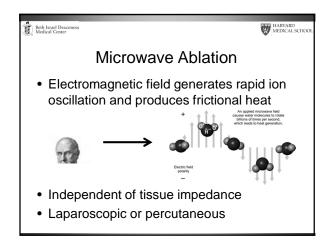


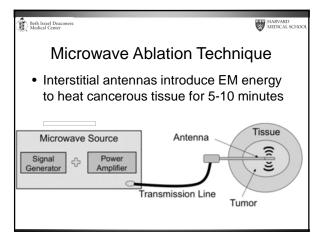


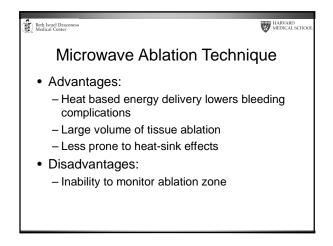


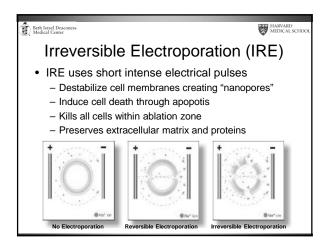


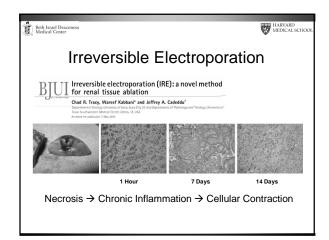


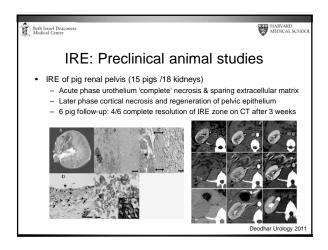


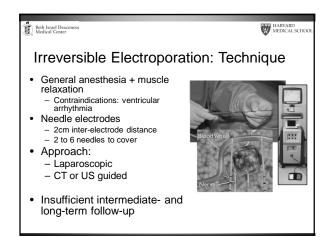




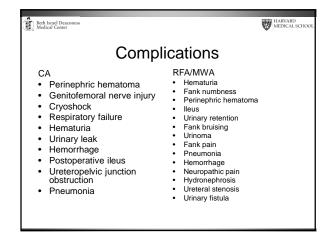


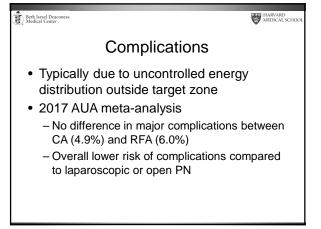


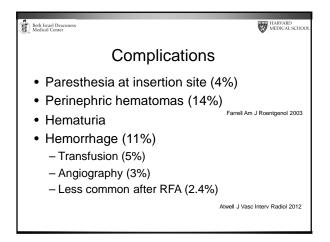


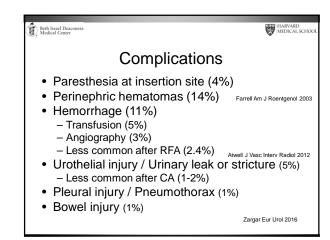


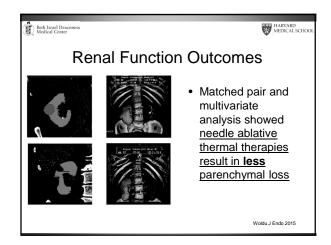


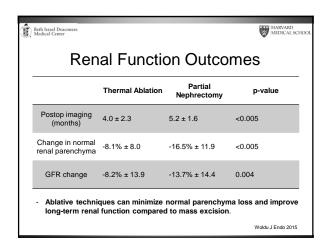


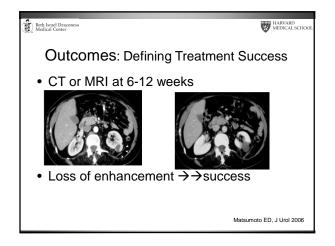


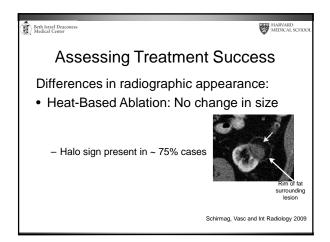


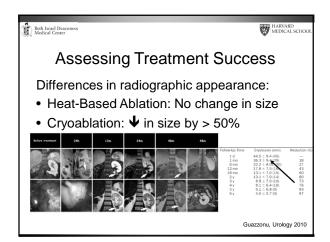


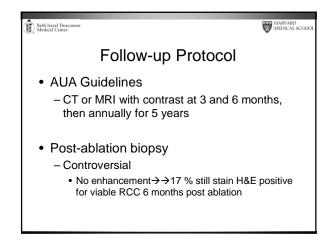


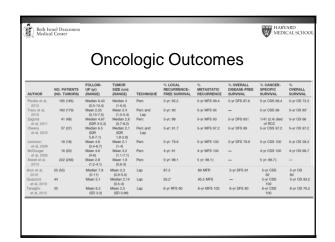


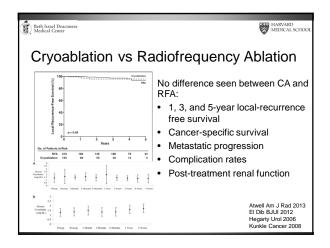


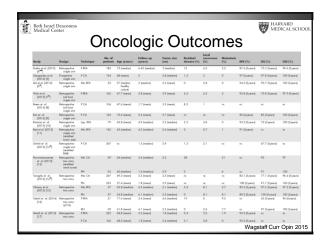


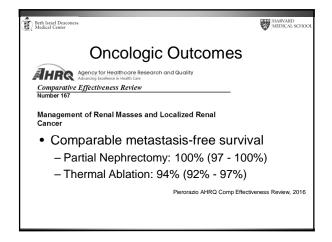


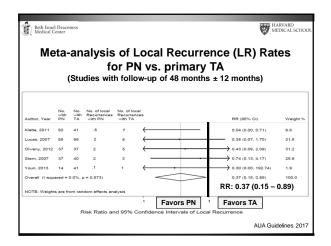


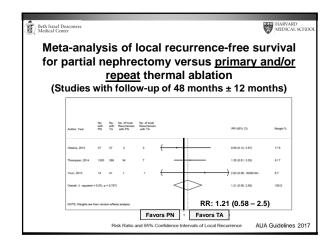






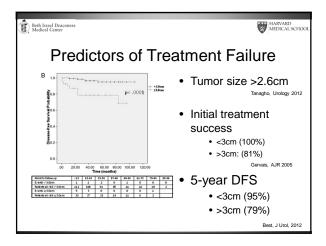


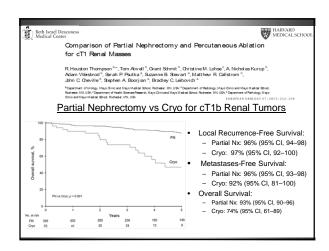


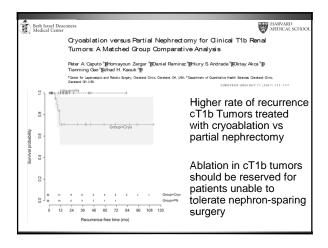


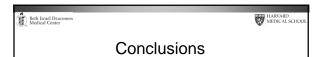


- Local recurrence free survival in favor of PN over TA
- When you include salvage treatment, then the effect is less obvious
- · No information is available on cystic lesions
- · So what predicts failure









- Minimally invasive options are expanding
- Partial Nephrectomy remains gold standard for NSS
- Long term oncologic f/u still required
- Ablative therapies may be appropriate in certain patient populations







### Acute kidney injury

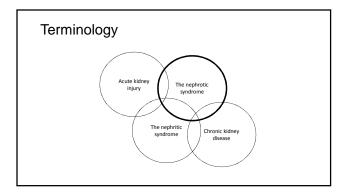
Melanie P. Hoenig Associate Professor Harvard Medical School Beth Israel Deaconess Medical Center

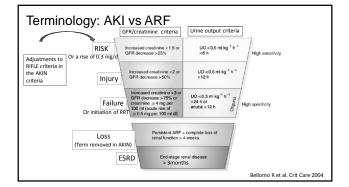
### Disclosure

• Editor for KSAP (Kidney Self Assessment Program), a board review and MOC product from American Society of Nephrology

### Acute kidney injury

- Review of terminology
- Categories of acute kidney injury:
  - Prerenal azotemia
  - Intrinsic renal disease
  - "post" renal
- Complications of AKI
- Management



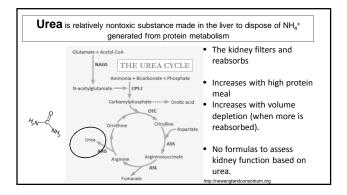


## Laboratory testing for assessment of kidney function

- Urine output
- BUN
- Creatinine
- Urinalysis
- Urine protein

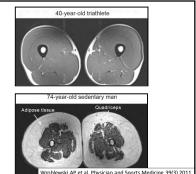
### Normal urine output

- Normal urine output ≈ 800-2liters/day
- •Oliguria is <500 ml/day or < 20 ml/hour (or 0.5 ml/kg/h)
- •Anuria is < 50 ml/day
- Polyuria is > 3L

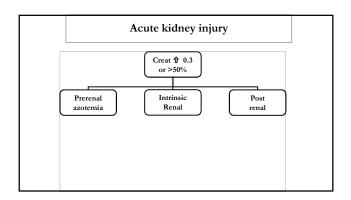


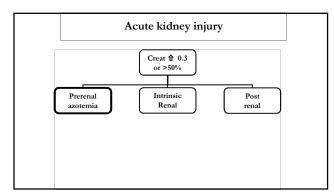
### Creatinine

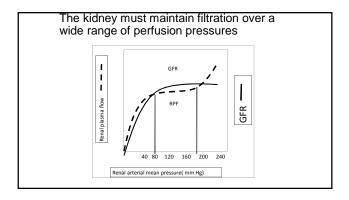
- generated from normal muscle metabolism.
- An average individual makes approximately 1 gram over course of a day.
- Those with more muscle mass will have slightly higher serum creatinine values and those with less will have lower values.

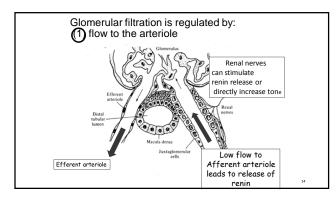


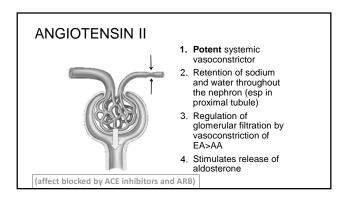


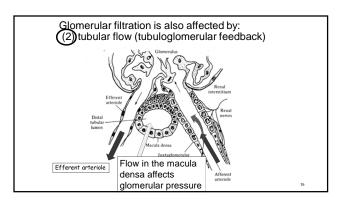


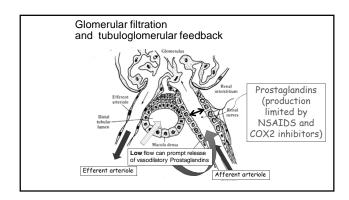












### **Characteristics of Prerenal azotemia**

1. Clinical history of volume depletion from losses or relative hypotension

### 2. Elevated BUN to creatinine ratio

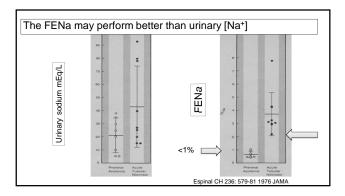
Volume Depletion

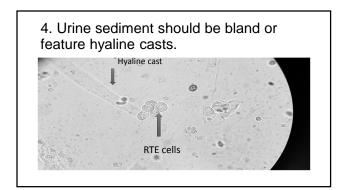
GI Bleeding Steroids-high catabolic rate

<u>BUN</u> Creatinine

High Protein intake

Low muscle mass (creatinine rises little)



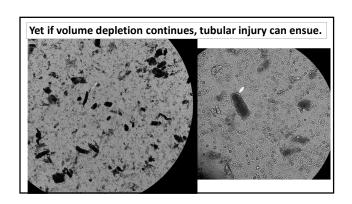


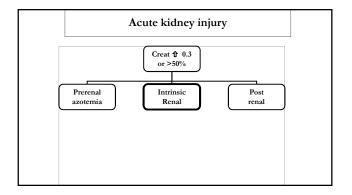
3. Low urinary sodium and/or FENa

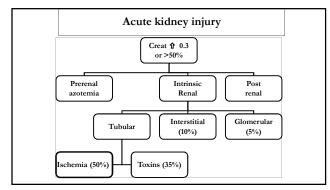
 $FE_{Na} = \quad U_{Na} * P_{Cr} \quad X \quad 100\%$ 

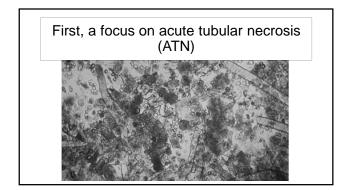
### Prerenal azotemia

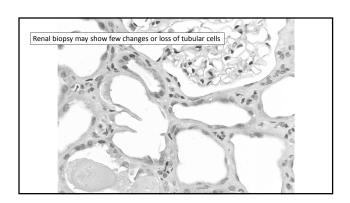
- High BUN to creatinine ratio
- Bland urinary sediment (or hyaline casts)
- Low urinary sodium
- Low FENa
- High urine osmolality (or specific gravity)











	Prerenal azotemia	ATN
urine sediment	Benign	Casts, tubular cells
Urine osmolarity	> 500 mOsm/L	< 350 mOsm/L
Urine [Na+]	< 10 mEq/L	> 20 mEq/L
FENa = <u>UNa/PNa</u> Ucreat/Pcreat	< 1 %	> 2 %

Tubular damage can also occur from toxic injury:

• Myoglobin

• Aminoglycosides

• Iodinated contrast

### Rhabdomyolysis with renal failure

### Case reports with

- 1. exaggerated lithotomy position
- 2. Laparoscopic donor nephrectomy or laparoscopic nephrectomy
- 3. Plus--Trauma victims who are also receiving urologic care

### Presentation:

severe muscle pain tea colored urine Elevated CPK

### Treatment:

Forced alkaline diuresis (or simply fluid resuscitation)

### **Contrast Induced Nephropathy (CIN)**

- Considerable decline in incidence with preventative measures
- Characterized by an abrupt decline in kidney function 24-48 hours after receiving intravenous iodinated contrast
- Results from combination of direct tubular toxicity and renal ischemia (secondary to renal vasoconstriction)
- Risk factors: diabetes mellitus, baseline renal impairment and volume depletion

### Precautions for iodinated contrast

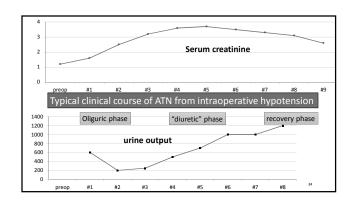
- Avoid studies with volume depletion
- Hold ACE I, ARB, diuretics and NSAIDS prior to procedure if possible
- IVF hydration

several protocols (ie Pre: 3cc/kg/hr X 1 hour; Post: 1cc/hr X6 hrs)

Consider N-Acetyl cysteine

• Non-ionic agents or "low" osmolar agents in smallest possible dose



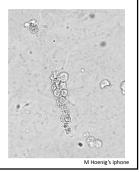


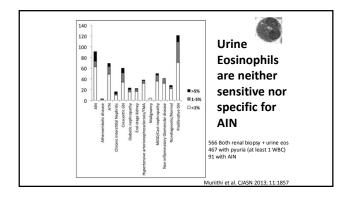
### Acute interstitial nephritis

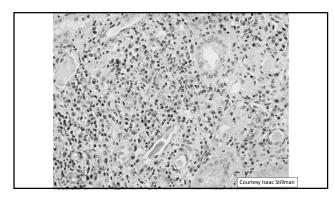
- Classic triad (for acute interstitial nephritis):
  - Rash 15%
  - Fever 27%
  - Eosinophilia 23%
  - All three 10%
- Decline in renal function
- Proteinuria usually mild

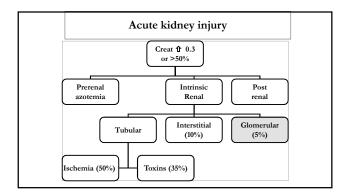
Baker RJ and Pusey CD NDT 2004 ; 19(1): 8-11 Summary of 3 small series= 128 patients

- Dipstick
  - Mild proteinuria
  - Isothenuria
  - ullet ± glycosuria
- Urine sedimentClassically:
  - WBC and WBC casts
  - Often bland









AKI is very uncommon in glomerular disease characterized by nephrotic syndrome

- Minimal change disease with heavy proteinuria
- Collapsing FSGS

### AKI does occur with Glomerulonephritis



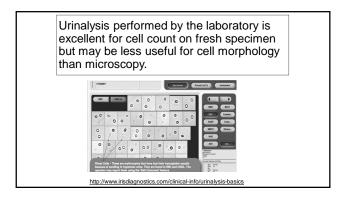
- Acute nephritic syndrome-days to weeks
- Rapidly Progressive Glomerulonephritis-weeks to months

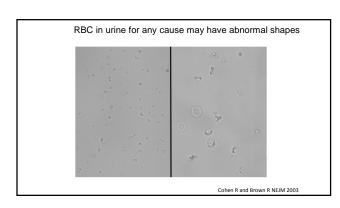
https://library.med.utah.edu/WebPath/TUTORIAL/URINE/URINE.htm

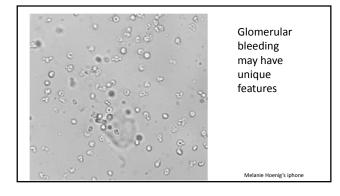
### AKI does occur with Glomerulonephritis

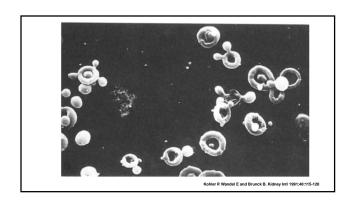
- Hallmark is an active urinary sediment: typically with acanthocytes, cellular casts
- Proteinuria
- Altered renal function
- Hypertension
- Potentially edema
- Multiple causes- symptoms depend on whether it is renal limited or systemic disorder and pace of clinical course

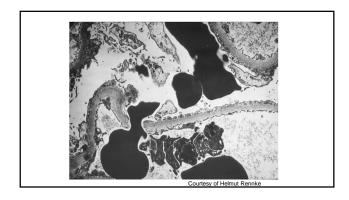
https://library.med.utah.edu/WebPath/TUTORIAL/URINE/URINE.html

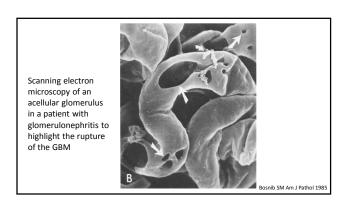


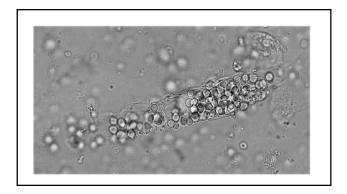


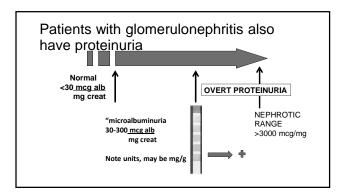












### "post renal" AKI

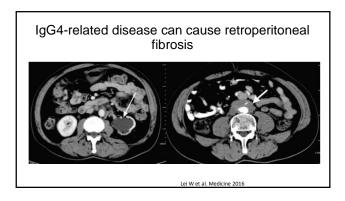
- Tubular obstruction by crystals
- Extrinsic obstruction
- Intraluminal obstruction

## "post renal" AKI Tubular obstruction by crystals Oxalate nephropathy (hyperoxaluria) Uric acid (tumor lysis syndrome) Exogenous agents such as protease inhibitors (indinavir, ralvetegravir) and acyclovir

### Extrinsic renal obstruction

- Malignancy-common
- Retroperitoneal fibrosis-rare

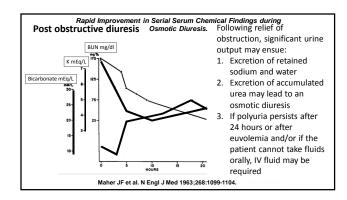
## A rare cause of extrinsic obstruction is IgG4-related disease

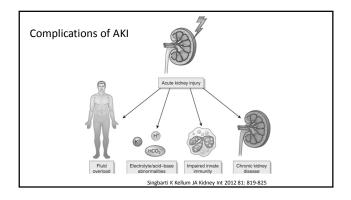




## Management issues following relief of obstruction

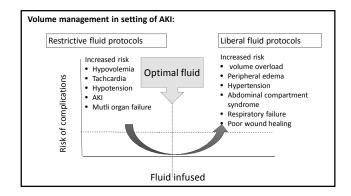
- Acute
  - Electrolytes
  - volume
- Chronic
  - Long term urologic management
  - Potential incomplete recovery of renal function

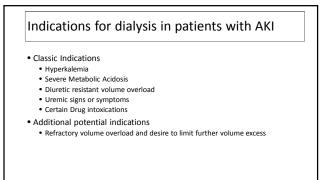




### Management of Patients with AKI

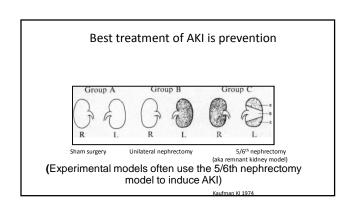
- Treat underlying cause when possible
- Discontinue all non-essential potential nephrotoxins
- Modify Drug dosages (may need to assume GFR=0)
- Review diet and IV fluid to avoid hyperkalemia, hyponatremia and metabolic acidosis
- Diuretics do not "convert" oliguric to non-oliguric but patients who respond may have better prognosis or easier management
- Kidney replacement therapy if necessary





## Prognosis for AKI varies by cause, comorbid conditions and prior renal function

- Prerenal azotemia is benign
- ATN in the ICU is more severe
  - 50 % mortality
  - 25% complete recovery
  - 20% incomplete
  - 5% no recovery



### Comprehensive Review of Urology

### **Chronic Kidney Disorders**

David Steele MD Renal Unit Massachusetts General Hospital Boston MA.

### **Disclosures**

• Reports no relationships with a commercial interest

### Aims

- Gather a sense of the demographics and natural history of Chronic Kidney Disease (CKD)
- Understand the impact of CKD on the patient and it's associated co-morbidities
- Review ESRD management options including medical management

### Nephrology Factoids





- Kidneys get  $^{\sim}$  20% of cardiac output
- Generate ultrafiltrate of 180L a
- Produce 1-1.5L urine output Excrete ~ 600-800 mosm
- Regulates
  - Volume (Na Metabolism)
  - Tonicity (Water Metabolism)
  - Potassium metabolism Acid/Base balance
  - Excretion of Nitrogenous wastes
  - Anemia (Erythropoetin) Bone metabolism (1 alpha Hydroxylase)
  - Blood pressure (Renin)

### Question

A 55 year-old man, with a history of type 2 diabetes (15 years), hypertension (3 years) dyslipidemia (5 years) and cardiovascular disease (myocardial infarction 3 years ago). He was recently diagnosed with CKD. His most recent labs reveal an eGFR of 45 ml/min/1.73m2 and an ACR of 38 mg/g.

Which of the following should be avoided?

- A. ACE and ARB in combination
- B. Daily low-dose aspirin
- C. NSAIDs
- D. Statins
- E. A and C

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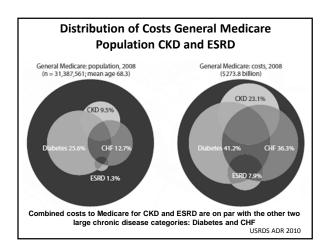
### **Answer**

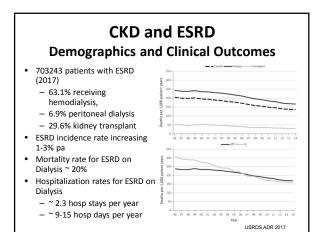
A 55 year-old Caucasian-American man, with a history of type 2 diabetes (15 years), hypertension (3 years) dyslipidemia (5 years) and cardiovascular disease (myocardial infarction 3 years ago). He was recently diagnosed with CKD. His most recent labs reveal an eGFR of 45 ml/min/1.73m2 and an ACR of 38 mg/g.

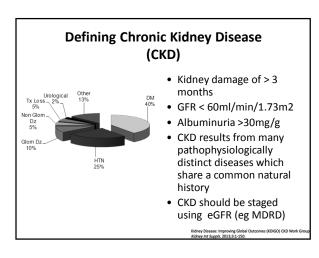
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www.kidney.org/CKDinform







### Question

- 69 y.o. male with CAD (four prior MIs), Heart Failure with Reduced Ejection Fraction (HFrEF) (EF=24%), severe Mitral Regurgitation, Paroxysmal Atrial Fib, Ventricular Tachycardia s/p ICD, Hypertension, Hyperlipidemia, CKD (baseline Cr 1.4), metastatic prostate cancer (on leuprolide), admitted for HFrEF exacerbation with course complicated by oliguric renal failure and concern for worsening cardiogenic shock, transferred to CCU for tailored therapy. Renal Artery Duplex Ultrasound negative for Renal Artery Stenosis. Renal function remains impaired despite optimizing CHF regimen. Work up of AKI should include:
- A. Repeat Renal Ultrasound
- B. Renal Biopsy
- C. Renal Nuclear Medicine Scan
- D. Upper extremity venous mapping for AV Fistula
- E. No additional work up needed

### **Answer**

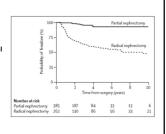
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- E. No additional work up needed

### Obstructive Uropathy

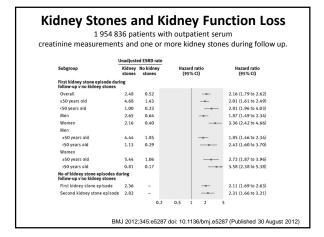
- Urinary tract obstruction should always be ruled out in patients with CKD and AKI on CKD
- In the absence of prostate disease renal perfusion is a much more likely cause of AKI/CKD
- Obstructive Uropathy is often asymptomatic
- If obstruction is present as the cause the urine sediment is often non diagnostic
- Recording bladder residual volume and dedicated renal ultrasound may be diagnostic

### Chronic kidney disease after nephrectomy in patients with renal cortical tumours

- Retrospective cohort study of 662 patients
- 3-year probability of freedom from new onset of GFR lower than 60 mL/min
  - 80% (95% CI 73-85) after partial nephrectomy 35% (28-43; p<0 0001) after radical nephrectomy;
- 3-year probability of freedom from new onset of GFRs lower than 45ml/min
  - 95% (91–98) after partial nephrectomy
  - 64% (56-70; p<0 0001) after radical nephrecotmy,



Huang et al Lancet Oncol 2006; 7: 735-40



### **Long-term Outcomes of Percutaneous Nephrolithotomy in Patients With Chronic Kidney Disease**

- Retrospective analysis of 69 PNL procedures in 67 patients
- PNL in patients with chronic kidney disease is safe and results in renal function preservation for a 5-year period.
- Diabetes mellitus and urinary infection were independent predictive of renal function impairment.



Mermet et al Urology 79 (5) May 2012

### The Acute and Long-Term Adverse Effects of Shock Wave

James A. McAteer, Ph.D. and Andrew P. Evan, Ph.D. Department of Anatomy and Cell Biology, Indiana University School of Medicine

- Intraparenchymal and subcapsular and hematomas
- Rupture of renal pelvis
- Proliferative glomerulopathy
- Anti-glomerular basement membrane disease
- Permanent loss of nephrons
- Diffuse fibrosis
- Acellular scarring from cortex to inner medulla
- Complete papillary necrosis
- Irreversible acute renal failure

Semin Nephrol. 2008 March; 28(2): 200-213

### Chronic kidney disease in urolithiasis patients following successful extracorporeal shockwave lithotripsy

SATOSHI MAEDA $^1,$  TOSHIHIDE NAGANUMA $^1,$  YOSHIAKI TAKEMOTO  $^1$  TETSUO SHOII  $^2,$  MIKIO OKAMURA  $^3$  and TATSUYA NAKATANI  $^1$ 

Compared 114 patients following successful ESWL and the 96 healthy control subjects
There was an increased prevalence of CKD among patients following ESWL
[40 patients (35.1%) vs. 9 healthy controls (9.4%), P<0.0001].

Variable	Unit increase	Unadjusted		Adjusted	
		Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Age	1 year	1.067 (1.028-1.107)	0.0006	-	-
Gender (males)		2.884 (1.170-7.107)	0.0214		
Hypertension		6.312 (1.253-6.211)	0.0424	2.011 (0.840-4.811)	0.1165
Diabetes mellitus		1.024 (0.432-2.428)	0.9568	0.711 (0.276-1.828)	0.4787
Dyslipidemia		0.694 (0.292-1.650)	0.2910	0.854 (0.324-2.249)	0.7488
Cardiovascular disease		1.806 (0.637-5.120)	0.2665	1.075 (0.334-3.462)	0.9032
Body mass index	$1 \text{ kg/m}^2$	1.107 (1.005-1.220)	0.0399	1.193 (1.058-1.345)	0.0039
Stone position (ureteric stone)		2.443 (1.093-5.461)	0.0295	2.612 (1.075-6.344)	0.0340
ESWL sessions (multiple)		1.105 (0.512-2.387)	0.7989	0.978 (0.419-2.285)	0.9590
Stone size (≥ 10mm)		0.696 (0.290-1.671)	0.4173	0.807 (0.310-2.100)	0.6593

MOLECULAR MEDICINE REPORTS 5: 3-6, 2012

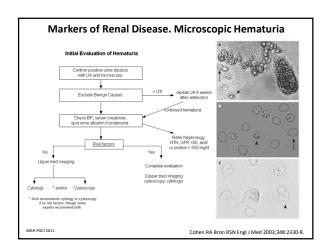
### Steps to CKD Patient Care

- 1. Does the patient have CKD?
  - Assess GFR, albuminuria.
- 2. Determine etiology.
- 3. Assess for evidence of progression.
- 4. Assess for associated complications.
- 5. Patient education.
- 6. Assess life expectancy and patient wishes for dialysis/transplantation.

### **Clinical Evaluation of Patients with CKD**

- Blood pressure
- HbA1c
- Serum creatinine
  - Use a GFR estimating equation or clearance measurement; don't rely on serum creatinine concentration alone.
  - Be attentive to changes in creatinine over time--even in "normal" range.
- Urinalysis
- Urine sediment
- Albuminuria/Proteinuria Spot urine for protein-to-creatinine or albumin-to-creatinine ratio.
- Electrolytes, blood glucose, CBC

- Depending on stage:
  - albumin, phosphate, calcium, iPTH
- Renal imaging
- Depending on age and н&Р
  - Light chain assay, serum or urine protein electrophoresis (SPEP, UPEP)
  - HIV, HCV, HBV tests
  - Complements, other serological testing - limited role unless specific reason



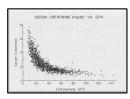
### **Markers of Renal Disease: Proteinuria**

- 24-hour urine not necessary
- "Spot" urine Protein (or Albumin) to Creatinine ratio recommended
- Example
  - Urine Protein155 mg/dl
  - Urine Cr 100 mg/dl
- Ratio = 155 mg/dl / 100 mg/dl
  - = 1550 mg/g creatinine
- Microalbuminuria
  - 30-300mg per 24 hrs Not detectable by dipstix
  - Marker of incipient renal disease
- Proteinuria
   300mg to 3.5grams per 24 hrs
   Marker of overt renal disease
  - Glomerular injury (usually Albumin)
     Tubulointerstitial (non Albumin)
- Nephrotic Range Proteinuria

  - > 3.5 grams
    Associated with Nephrotic Syndrome
    - Hypoalbuminemia Edema

    - Hyperlipidemia

### **Markers of Renal Disease: Serum** Creatinine



Age (Years)	Average Measured GFF (mL/min/1.73 m²)		
20-29	116		
30-39	107		
40-49	99		
50-59	93		
60-69	85		
70+	75		

Age	Weight in Ibs Height in Ft/in	Sex		SCr mg/dl	eGFR ml/ min per CKD-EPI	eGFR Adj for BSA
25	285 6'	м	AA	1.6	68	97
49	180 5'4"	F	Hispanic	1.6	38	41
67	155 5'8"	м	Asian	1.6	44	46
92	98 5'1"	F	Caucasian	1.6	28	22

### MDRD Equation (mL/min/1.73 m<sup>2</sup>) GFR = 175 × (S<sub>cr</sub>)<sup>-1.154</sup> × (Age)<sup>-0.203</sup> × (0.742 if female) × (1.212 if African American)

CKD Epi Equation (mL/min/1.73 m<sup>2</sup>)  $\begin{aligned} \mathsf{GFR} &= 141 \times \mathsf{min} \; (\mathsf{S}_{\mathsf{cr}} \, / \kappa, \, 1)^{\alpha} \times \mathsf{max} (\mathsf{S}_{\mathsf{cr}} \, / \kappa, \\ 1)^{-1.209} \times 0.993^{\mathsf{Age}} \times 1.018 \; [\mathsf{if} \; \mathsf{female}] \times \end{aligned}$ 1.159 [if black]

### **Evaluating CKD** Assign Albuminuria Category A3 >300 Severely increased\*\* \*Relative to young adult level. ACR 30-300 mg/g for >3 months indicates CKD. on ACR >2220 mg/g). ≥90 Normal or high 45-59 Mildly to moderate Assign GFR Category

### Question

All of the following adult patients should be referred for nephrology consultation, EXCEPT?

- A. Initial visit: eGFR 26 & 3 months later: eGFR 28 (mL/min/1.73m2)
- B. Initial visit: eGFR 55, & 3 months later: eGFR 43 confirmed with repeat eGFR 45 (mL/min/1.73m2)
- C. Initial visit: ACR 450 & 3 months later: ACR 355 (mg/g) on both dates the eGFR >60 mL/min/1.73m2
- D. Initial visit: eGFR >60 & 3 months later: eGFR >60 (mL/min/1.73m2) with personal history of Autosomal Dominant Polycystic Kidney Disease
- E. Initial visit: eGFR 42 & 3 months later: eGFR 44 (mL/min/1.73m2) on both dates the ACR <30 mg/g

www.kidney.org/CKDinform

### Answer

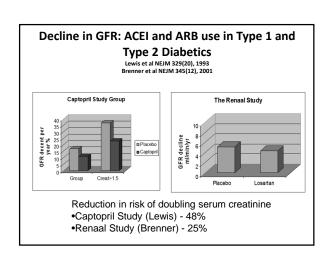
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www.kidney.org/CKDinform

	Categories: "Heat Map"						
					minuria catego		
CKD	CKD is classified based on:  • Cause (C)		A1	A2	A3		
GFR (G) Albuminuria (A)			Normal to mildly increased	Moderately increased	Severely increased		
			<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol		
	G1	Normal or high	290	1 if CKD	Monitor 1	Refer*	
.m 27.	C		1 if CKD	Monitor 1	Refer*		
(mVmin/1			Monitor 1	Monitor 2	Refer 3		
agproes			Monitor 2	Monitor 3	Refer 3		
18 8	G4	Severely decreased	15-29	Refer*	Refer*	Refer 4+	
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+	
Colors: Represents the risk for progression, morbidity and mortality by color from best to worst. <u>Green:</u> low risk (if no other markers of kidney disease, no CKD); <u>Yellow:</u> moderately increased risk; <u>Orange</u> : high risk; <u>Ged, very high risk</u>							
	Numbers: Represent a recommendation for the number of times per year the patient should be monitored.						
Refer: Indicates that nephrology referral and services are recommended.							

### **Progression of CKD** - Angiotensin II effects Primary Injury with loss of Nephron mass Angiotensin II Hemodynamic effects Hyperfiltration of · Single nephron increased emaining healthy Nephrons GFR Increased intraglomerular pressure Non Hemodynamic effects • Inflammation and · Cellular hypertrophy and proliferation Secondary Focal Segmental Glomerulosclerosis



### **ACEI/ARB's in CKD**

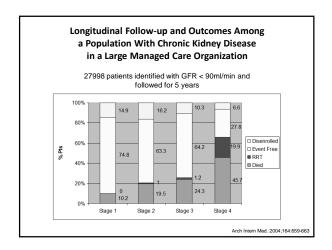
- ACEI or ARB are indicated for diabetic patients with uAlb/Creat ratio>0.03 (microalbuminuria)
- ACEI or ARB are indicated for CKD patients with uAlb/Creat ratio>0.5 (overt proteinuria)
- ACEI or ARB are indicated 1. Tolerate a small (15-20%) rise for diabetic patients with in serum creatinine
  - 2. Attempt to manage Hyperkalemia without withdrawal of ACEI/ARB:
    - Dietary K restriction
    - Gastrointestinal potassium binders prn
    - Loop diuretics; Fludrocortisone
  - 3. Use ARB in patients intolerant to ACEI (cough)

### Question

- The Tromsø study looked at the natural history of CKD in a population of 58000 patients in Scandinavia. 3047 patients were found to have a GFR between 30 and 60 ml/min. Patients were followed for 10 years and the rate of progression to ESRD was:
- A. 4%
- B. 10%
- C. 12%
- D. 25%

### **Answer**

- The Tromsø study looked at the natural history of CKD in a population of 58000 patients in Scandinavia. 3047 patients were found to have a GFR between 30 and 60 ml/min. Patients were followed for 10 years and the rate of progression to ESRD was:
- 4%
- B. 10%
- C. 12%
- D. 25%



### Strategies for Caring with Patients with CKD 4

- Delay Progression
  - ACF Inhibition
  - Manage metabolic abnormalities
  - Minimize AKI risk
  - Review dietary options
- Manage Comorbids
  - Cardiovascular risk
  - Anemia management
  - Metabolic Bone Disease Management
- · Prepare for **FSRD** 
  - Isolate high risk
  - populations Patient
  - education
  - Refer to Nephrology
  - Prepare for angioaccess
  - Review Medical Management options

### **Diet and Lifestyle**

- CKD patients should receive expert dietary advice if available
- Lower protein intake to 0.8 g/kg/day in patients with GFR <30 ml/min
- Avoid high protein intake (>1.3 g/kg/day) in adults with CKD at risk of progression.
- Target HbA1c of <7.0% (extended above 7.0% in individuals with comorbidities or limited life expectancy and risk of hypoglycemia)
- Lower salt intake to <2 g per day of

### <u>Lifestyle</u>

- Undertake physical activity 30 minutes 5 times per v
- Achieve a healthy weight
- BMI 20 to 25 · Stop smoking
- Avoid NSAID's

### **Vaccinations**

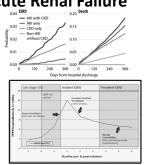
- Annual Influenza
- Pneumococcal vaccine q 5 vears
- Hepatitis B for stage 5 CKD and likely progression to HD

Kidney International Supplements (2013) 3, 5-14

### **CKD** predisposes hospitalized patients to Acute Renal Failure

- · CKD increases the risk of AKI seven fold in hospitalized patients.
- In AKI patients with CKD, the hazards for:
  - ESRD 85.0
  - Death 3.1

(in AKI patients with no CKD, hazards are 11.7 and 2.5, respectively)



These are the patients who "crash" onto dialysis

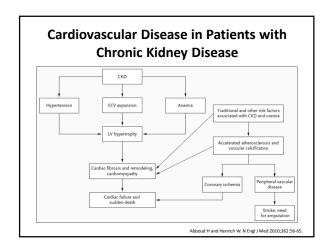
### NephroPharmacology

Renally dose all medications and monitor eGFR and drug levels as indicated.

- Reconsider dose with any significant change in eGFR and review medications regularly for continued appropriateness.
- Prolonged NSAID use should be avoided in early stage CKD.
- Counsel patients to consult a physician or pharmacist before using over-the-counter medications or supplements.

Consider monitoring eGFR more frequently and holding renally cleared and potentially nephrotoxic medications during acute illness or in the perioperative period.

## Imaging Studies Iodinated Contrast Studies: Avoid high osmolar agents Use lowest possible contrast dose compatible with complete study Withdraw potentially nephrotoxic agents before and after the procedure Give adequate hydration with saline before, during, and after the procedure Measure GFR 48–96 hours after the procedure Gadolinium-based contrast studies: Do not use gadolinium in Pts with GFR <15 ml/min/1.73 m2 (unless there is no alternative appropriate test) For pts with a GFR <30 ml/min use a macrocyclic chelate preparation Bowel preparation: Avoid oral phosphate-containing bowel preparations in pts with GFR <60 ml/min due to risk of phosphate nephropathy



### **Management of HTN**

### **JNC 8:**

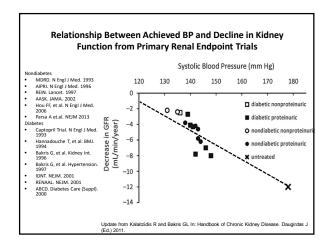
- In the general population aged ≥60 years
  - Treat BP > 150/90
- In the general population <60 years
  - Treat BP > 140/90
- In the population aged ≥18 years with CKD
  - Treat BP > 140/90 and use ACEI or ARB

### **KDIGO Guidelines:**

- In diabetic and nondiabetic adults with CKD and with urine albumin excretion of >30 mg/24 hours
  - Treat BP >130/80 and use ACEI/ARB

(2D level of evidence)

JAMA February 5, 2014 Volume 311, Number 5



### **Anemia Management**

- Check hemoglobin in patients with eGFR < 45 ml/min</li>
- Exclude other causes of anemia before attributing to CKD
- If the patient is likely to benefit in terms of quality of life, consider referral for ESA candidacy if Hb < 9g/dl</li>

## Studies of Anemia Management and the use of Erythropoetin in CKD

Normal Hct Study Besarab A et al. N Engl J Med 1998;339:584-590	183 deaths and 19 non fatal MI's in nI-Hct group and 150 deaths and 14 non fatal MI's in low-Hct group (RR 1.3; 95% CI, 0.9 to 1.9). Study halted.	Pts in nl-Hct group had a decline in the adequacy of dialysis and received more IV iron dextran.
CHOIR Study Ajay Singh et al. N Engl J Med 2006;355:2085-98.	125 events (Death, MI, CHF, Stroke) in the high-Hb group vs 97 events in the low-Hb group (HR, 1.34; 95% CI, 1.03 to 1.74; P = 0.03).	Improvements in the quality of life were similar in the two groups.
CREATE Study Drueke et al N Engl J Med 2006;355:2071-84	No effect on first cardiovascular event	General health and physical function improved significantly (P = 0.003 and P<0.001) in high Hb group.
TREAT Study Marc Pfeffer et al N Engl J Med 2009;361:2019-32	Death or a cardiovascular event in 632 pts in Rx group vs 602 pts in placebo group (P = 0.41)	Fatal or nonfatal stroke in 101 pts in Rx grp vs 53 in placebo group (P<0.001).

### Vascular Biology is abnormal in CKD.

Coronary-Artery Calcification in Young Adults with End-Stage Renal Disease Undergoing Dialysis

(N Engl J Med 2000;342:1478-83. AIN May 1998 Vol 128:10; 839-847)



Sample electron-beam computed tomographic scan showing calcification of the left anterior descending coronary artery (thick arrow) and the aortic root (thin arrow).

- Coronary-artery calcification is common and progressive in young adults with end-stage renal disease who are undergoing dialysis.
- The mean serum phosphorus, the mean calcium-phosphorus ion product, and the daily intake of calcium were higher among the patients with coronary-artery calcification

### Mineral Metabolism in CKD

Measure serum calcium and phosphate if eGFR < 45ml/min

Avoid	Correct Nutritional	Treat Secondary
Hyperphosphatemia	25OH Vit D Deficiency	Hyperparathyroidism
Restrict dietary phosphate intake Use phosphate binders when indicated -Calcium based: CaCO3; Ca Acetate -Non Calcium Based Sevelamer; (AIOH3)	Supplement with 250H Vit D if level <30ng/L Eg: Ergocalciferol 50000u/week for 12 weeks	Supplement 1,25 Vitamin D (Calcitriol) according to PTH level Treat with Calcitriol or equivalent if: - PTH > 70ng/L in CKD 3 - PTH > 120ng/L in CKD 4

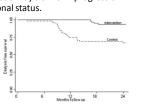
Offer bisphosphonates for the prevention and treatment of osteoporosis in patients with eGFR > 30 ml/min on the same indications as for all other patients

### Metabolic Acidosis

- Often becomes apparent at GFR <25-30 ml/min/1.73m2.
- More severe with higher protein intake.
- May contribute to bone disease, protein catabolism, and progression of CKD.
- Correction of metabolic acidosis may slow CKD progression and improve patients functional status.

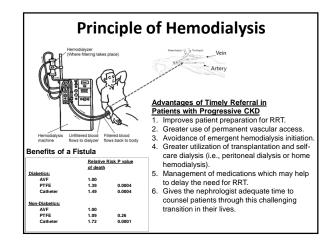
Adults with CKD 4 (eGFR 15-30)with bicarbonate 16-20 mmol/L; treated with sodium bicarbonate.

Mahajan, et al. Kidney Int. 2010;78:303-309.
 de Brito-Ashurst I, et al. J Am Soc Nephrol. 2009;20:2075-

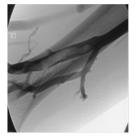


## Preparing for ESRD: Patient and Physician Awareness Patient awareness Coresh, et al., 2007 Physician Awareness McClellan, AIKD 1997, 29:368-75 Mode James Coresh and Cores Core

## Preparing for ESRD: The Timing of Specialist Evaluation in Chronic Kidney Disease; effect on Morbidity and Mortality Effect of timing of referral on length of stay at the initiation of dialysis Rate of death measured from initiation of dialysis to average of 2.2 years follow up



### Thrombosis following PICC placement



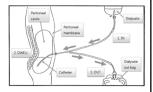
Allen et al, JIVR, 2000

- Identify CKD stages 3B,4 or 5, including current hemodialysis, peritoneal dialysis or transplant patients as a special population when planning central venous access
- Plan appropriate venous access in these cases
  - dorsal hand veins for phlebotomy
  - internal jugular veins are preferred for central venous access
  - external jugular veins are acceptable alternative
  - Avoid any catheters in subclavian veins

### **Peritoneal Dialysis**

- Less than 8% of prevalent ESRD patients in the US are on PD; significantly less than in other developed countries
  - subtle differences in practice patterns unintended financial considerations
- Medical outcome date would seem to favor more utilization of PD
- Improved mortality Most home dialysis units are small
- some have minimal clinical experience
- consolidation of PD programs may

Burkhart J, CJASN 2009 Dec;4 Suppl 1:S125-31



Multidisciplinary pre-dialysis programs increase the proportion of patients initiating dialysis with PD.

Ribitisch et al Peritonal Dial Int 2013 Jul-Aug;33(4):367-7

### **Kidney Transplantation**

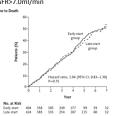
Iliac Fossa

**Key Concepts** 

- · Kidney transplantation is the most cost
  - effective modality of renal replacement.
    - · Transplanted patients have a longer life and better quality of life.
  - Early transplantation (before [pre-emptive] or within 1 year of dialysis initiation) yields the best results.
  - Living donor kidney outcomes are superior to eased donor kidney outcome
  - Early transplantation is more likely to occur in patients that are referred early to nephrologists.
- Refer for transplant evaluation when eGFR <20 mL/min/1.73m2.

### Timing of the initiation of dialysis: **Early versus Late Start.**

- 828 patients
- Early Start: GFR 10-14ml/min; Late Start: GFR 5-7ml/min
- 76% of late start patients initiated HD with GFR>7.0ml/min



before/when one or more of following is present:

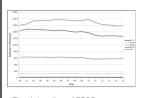
- Symptoms or signs attributable to kidney failure (serositis, acidbase or electrolyte abnormalities, pruritus);
- Inability to control volume status or blood pressure;
- Progressive deterioration in nutritional status refractory to dietary intervention;
- Cognitive impairment

Often occurs in the GFR range between 7 and 10 ml/min

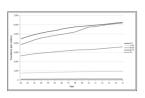
N Engl | Med 2010;363:609-19

### Incidence of ESRD: By Age

- the ageing of the dialysis population



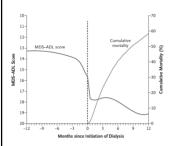
Trends in adjusted ESRD incidence rate, by age group, in the U.S. population, 2000-2015



Trends in the adjusted prevalence of ESRD, by age group, in the U.S. population, 2000-2015

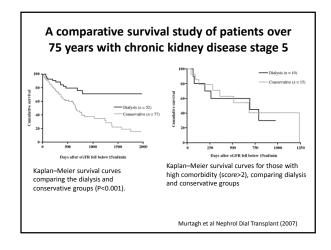
USRDS ADR 2018

## **Functional Status of Elderly Adults** before and after Initiation of Dialysis



- •3702 nursing home residents in the United States •Initiated dialysis dialysis between June 1998 and October 2000.
- •At least one measurement of functional status was available before dialysis.
  •Functional status was measured
- by assessing the degree of dependence in seven ADL's (on the Minimum Data Set-Activities of Daily Living [MDS-ADL] scale of 0 to 28 points, with higher scores indicating greater functional

Tamura et al N Engl J Med 2009;361:1539-47.



## Conservative Management of Stage V CKD

- Conservative management should be an option
- It should be supported by a comprehensive management program.
- It should be available to people and families through either primary care or specialist care as local circumstances dictate.
- The comprehensive conservative management program should include:
  - protocols for symptom and pain management,
  - psychological care, spiritual
  - culturally sensitive care for the dying patient and their family (whether at home, in a hospice or a hospital setting)
  - provision of culturally appropriate bereavement support.

Kidney International Supplements (2013) 3, 5-14

### **Conclusions**

- Kidney Disease is common and management is complicated
- The majority of patients with CKD have non progressive disease.
- Cardiovascular disease is a major co-morbidity
- For patients with progressive CKD care strategies should be initiated early to improve long term morbidity and mortality
- A team approach is required
- Pre-planning for renal replacement therapies is necessary in those with progressive disease

## Cancer of the Renal Pelvis and Ureter

Vitaly Margulis, MD

Associate Professor
Department of Urology
UT Southwestern Medical Center

### Disclosure:

Dr. Margulis has nothing to disclose

- Introduction
- Etiology
- Clinical Features
- Imaging Diagnosis
- Confirmatory Diagnosis
- Staging
- Risk stratification
- Treatment Guidelines
- Radical Nephroureterectomy
- Management of Bladder Cuff
- Lymphadenectomy
- Conservative Surgical Approaches
- Mx of upper tract positive cytology/CIS
- Adjuvant Therapy
- Treatment of Metastaic Disease
- Follow up protocol

### Transitional Cell Carcinoma

- Originates from Transitional epithelium of urinary to
- Most common in urinary bladder, then in renal pelv least in ureter(125:2.5:1)
- 5-10% of upper urinary tract neoplasms.
- Renal TCC most common --extrarenal part of the properties of the proper
- 2%–4% ---bilaterally.

### Relation with Bladder TCC

- Upper tract TCC after bladder TCC- 2-49
- Bladder TCC after Upper tract TCC- 15-

### **ETIOLOGY**

- Genetic
  - Hereditary UTUC is associated with hereditary nonpolyp colorectal carcinoma (HNPCC), or Lynch syndrome.
- Environmental
  - Balkan Nephropathy/ Chinese herb nephropathy: Aristolo acid, which is found in plants Aristolochia fangchi and Aristolochia clematitis, has a mutagenic action on codon p53 gene.
  - Smoking: Aromatic amines.
  - Analgesic abuse
    - Phenacetin- 2yrs latent phase
    - Acetoaminophin- 20 yrs latent phase.
  - Arsenic exposure
  - Occupational
    - 7 yrs of contact/inhalation to aromatic amines.

### Clinical features

- most common in 7<sup>th</sup> decade, rare in childhood
- males 3 times > female

### Clinical features

- Hematuria- gross/ microscopic- 56-95%
- flank pain or acute renal colic(clots)
- discovered incidentally at radiologic examination- 15%

### **IMAGING MODALITIES**

### INTRAVENOUS UROGRAPHY

- Supplanted by CT-IVU
- detailed anatomy of the pelvicalyceal system and ureters.

- a filling defect within the contrast-enhanced collecting system, single or multiple & smooth, irregular or stippled
- Stipple sign---tracking of contrast material into the interstices of a papillary lesion
- Tumor-filled, distended calyces -- "oncocalyces."
- If these fail to opacify with contrast-- "phantom calyces."

### **Computed Tomography**

 CT is well established in the preoperative staging and assessment of upper tract TCC- 100% sensitivity and 60%specificity.

### CT urography

- single breath-hold coverage of the entire urinary tract,
- has improved resolution
- has the ability to capture multiple phases of contrast material excretion

- Hydronephrosis and hydroureter
- Ureteric TCC-- Ureteric wall thickening (eccentric or circumferential), luminal narrowing, or an infiltrating mass.
- A thickened enhancing ureteric wall with periureteric fat stranding -- suggestive of extramural spread

### **Pre-op Confirmation**

- Cystoscopy Mandatory to rule out concurrent bladder tumor.
- Ureteroscopy
  - Reserved for doubtful cases (On radiology)
  - Brush or punch biospy
  - Staging not accurate as depth of tumor not well assesed
  - Risks of tumor seeding, extravasation, and dissemination- Low but present

### Retrograde Pyelography

### 75% Sensitivity

- in inadequately excreting kidneys,
- in cases of contrast allergy.
- facilitates ureterorendoscopy with biopsy or brushing & cytology of urine
- an intraluminal filling defect, -- smooth, irregular, or stippled.

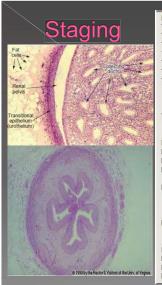
- An "apple core" appearance-- eccentric or encircling ureteric lesions
- localized ureteric dilatation around and distal to the filling defect may give rise to the "goblet" sign.

### Cytology and Tumor Markers

- Sensitivity
  - 20% for grade 1 tumors
  - 45% for grade 2
  - 75% for grade 3 tumors
- If a voided cytology specimen is abnormal in a patient with an upper tract filling defect-
  - Ureteral catheterization
  - Washings from ureter more accurate
  - Brush biopsy- Sensitivity in the 90%
    - Massive hemorrhage
    - Perforation of the urinary tract with extravasation

### FISH in TCC- Upper and Lower

• FISH probes were used for chromosomes 3, 7, 17, and the *CDKN2A* (9p21) gene, overall sensitivity of FISH was significantly higher than that of cytology and specificity for both was 100%



### Primary tumor cannot be assessed. No evidence of primary tumor. TX T0 Ta Tis T1 T2 Papillary noninvasive carcinoma. Tumor invades subepithelial connective tissue Tumor invades the muscularis. Тз Tumor invades periureteral fat (for renal pelvis Tumor invades beyond muscularis into perinephric fat or the renal parenchyma. Tumor invades adjacent organ or through the kidney into the perinephric fat. LYMPH NODES (N) Regional lymph nodes cannot be assessed. No No regional lymph node metastases Metastasis to a single lymph node, 2 cm or less in greatest dimension. Metastasis in a single lymph node, more than N2 2 cm but not more than 5 cm in greatest

DISTANT METASTASIS (M)

Distant metastasis cannot be assessed.

in greatest dimension.

dimension; or multiple lymph nodes, none more than 5 cm in greatest dimension. Metastasis in a lymph node, more than 5 cm

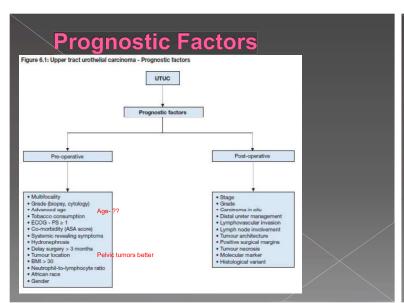
No distant metastasis. Distant metastasis.

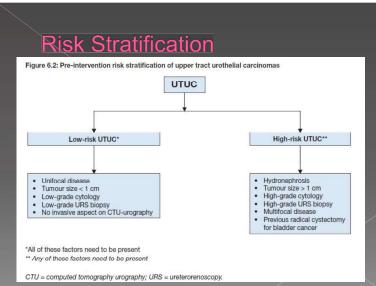
### Histologically

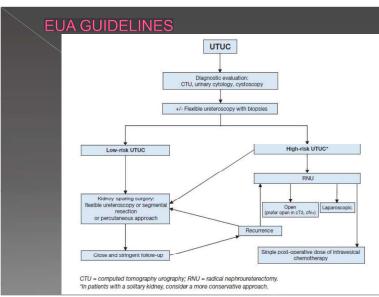
- TCC- Most common
- Variant Histology
  - > Squamous- Ch. Infection, inflamation or analgesic abuse
  - Glandular
  - Sarcomatoid
  - Neuroendocrine
    - Micropapillary- Aggressive and poor prognosis

### Tumor spreads by

- mucosal extension
- local
- Hematogenous
- lymphatic invasion
- The most common sites for metastases are the lungs, liver, bones, and regional lymph nodes.







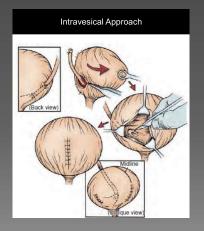
# Open Radical Nephroureterectomy Dissection outside gerota's Adrenal removed only if found involved on pre-op imaging or intra-operatively. Management of Distal Ureter and Bladder Cuff The entire distal ureter, including the intramural portion and the ureteral orifice, has to be removed

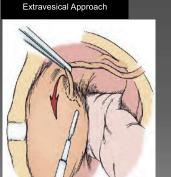


### Importance of Complete Resection

• The risk of tumor recurrence in a remaining ureteral stump is 30% to 75%

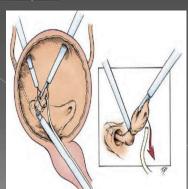
### **Traditional Open Distal Ureterectomy**





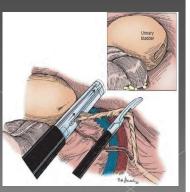
### Transvesical Ligation and Detachment Technique

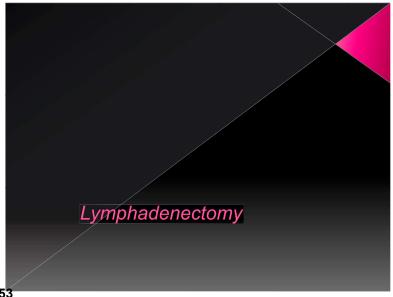
- Low lithotomy position
- Cystoscopy- bladder filled.
  One or two 5-mm trocars are placed intravesically from the suprapubic
- Endoloop is placed around the ureteral orifice, and a ureteral catheter is advanced into the ureter through the Endoloop.
- through the Endoloop.
  With a Collins knife the bladder cuff is incised, and this incision is carried into the extravesical space.
  Retraction is provided by the grasper through one of the trocars.
  Once the ureter is freed, the Endoloop is cinched around the ureter as the catheter is removed.



### Total Laparoscopic Technique

- Initial cystoscopy Placement of a ureteral catheter and incision of an intramural tunnel at the 12 o'clock position Ureteral orifice is cauterized
- After nephrectomy the distal ureter is traced to detrusor muscle. The detrusor muscle is split and the ureter retracted in antegrade direction. The endovascular stapler is then used to place a staple line as distally as possible
- A fulguration mark helps serve as an identifier of the bladder cuff

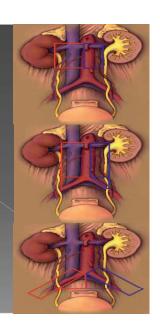


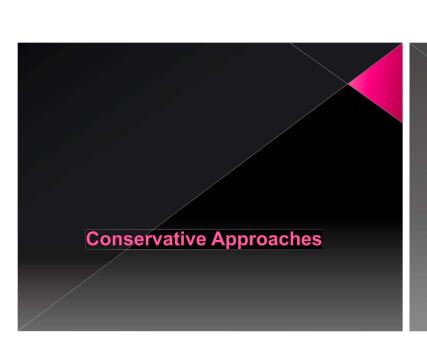


## The role and extent of lymphadenectomy

 Limited or regional lymphadenectomy is included with radical nephroureterectomy

- For renal pelvis- lpsilateral hilar nodes +
  - Right-sided tumors paracaval, retrocaval, and interaortocaval lymph nodes
  - For left sided tumors- paraaortic lymph nodes
  - The inferior mesenteric artery marks the inferior boundary of the template.
- For upper two thirds of the ureter- Template is extended to the level of bifurcation of aorta
- For distal ureter- Ipsilateral common, external and internal iliac, obturator, and presacral nodes.





## **Open Nephron**-Sparing Surgery for Renal Pelvis Tumors

- The risk of recurrence after conservative surgery
  - Grade 1 less than 10%
  - > Grade 2- 28%
  - Grade 3 60%

### Open Segmental Ureterectomy

- Ureteroureterostomy
  - Proximal ureter or midureter
  - 1-2 cm margin proximally and distally
- Distal Ureterectomy and Direct Neocystostomy or Ureteroneocystostomy with a Bladder Psoas Muscle Hitch or a Boari Flap
- Ileal Ureteral Replacement
- Renal autotransplantation

- Segmental ureterectomy is offered for lowgrade, non-muscle-invasive disease of the proximal ureter or mid-ureter that is not amenable to complete ablation by endoscopic means because of tumor size or multiplicity.
- Distal ureterectomy and neocystostomy may be offered for low-grade, low-stage, or in select cases, high-grade, locally invasive tumors of the distal ureter when renal preservation is necessary.

### Open v/s Endoscopic Management

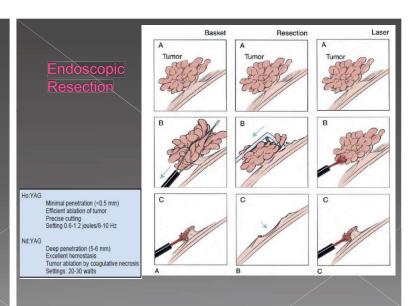
- The advantage of a ureteroscopic approach is lower morbidity than that of the percutaneous and open surgical counterparts, with the maintenance of a closed system.
- With a closed system, nonurothelial surfaces are not exposed to the possibility of tumor seeding.

### **Endoscopic Management**

- Indications
  - Unifocal Disease
  - Low Grade tumor
  - Low volume tumor < 1cm
  - Non invasive on CT- IVU
  - Abnormal kidney Opposite
    - Bilateral tumor
    - CKD
    - Higher risk for CKD
  - Poor surgical risk

### Antegrade v/s Retrograde Mx

- Retrograde
  - Smaller instruments smaller field of view and working channel- Removal of bulky tumors not possible
  - Difficulty in accessing the lower pole
  - Difficult in patients with prior urinary diversion.
- Percutaneous
  - Large volume tumor can be resected
  - Higher morbidity
  - Better in complicated calyceal and lower pole calyx
  - Nephrostomy tract can be maintained for immediate postoperative nephroscopy and administration of topical adjuvant therapy



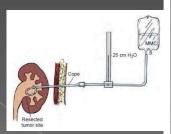


- After Organ-Sparing Therapy
  - Instillation Therapy
    - Immunotherapeutic Agent
    - Chemotherapeutic Agent
- After Complete Excision
  - Radiation Therapy
  - Systemic Chemotherapy

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# After Organ-Sparing Therapy

- Instillation Therapy- Primary treatment for CIS and as adjuvant therapy after endoscopic or organ-sparing therapy.
  - Thiotepa
  - Mitomycin
  - BCG
  - Gemcitabine alternative to BCG with fewer side effects
- **Brachytherapy** To nephrostomy tract through iridium wire or delivery systemdescribed by Patel and coworkers (1996) and Nurse and colleagues (1989). No recurrences. Complication-Cutaneous fistula formation requiring nephroureterectomy.



- 1: Nephrostomy tube

 Ureteric catheter
 Ureteral stent or
by iatrogenically created vesicoureteral reflux- Not reliable

# After Complete Excision

- Radiation Therap
  - For Stage T3 to T4, N+
  - Radical nephroureterectomy alone provides a high rate of local control. Adjuvant radiation without chemotherapy for high-stage disease does not protect against a high rate of distant failure.
  - There may be a role for combined radiationchemotherapy regimens in patients with advanced disease with adverse features; however, the current evidence supporting this is small and retrospective in

# Systemic Chemotherapy

- - MVAC (methotrexate, vinblastine, Adriamycin, and cisplatin),
  - MEC (methotrexate, etoposide, and cisplatin)
  - MVEC (methotrexate, vinblastine, epirubicin, and cisplatin)
  - gemcitabine-paclitaxel-doxorubicin [GTA]
  - Cisplatin-gemcitabine[GC]
- Adjuvant Chemotherapy
- Lack of controlled trials that establish the efficacy of either neoadjuvant or adjuvant chemotherapy in this UTUC. However, given the significant influence of renal function on eligibility to receive effective chemotherapy, the focus is shifting toward a neoadjuvant approach, with several trials underway.
- Further studies are needed to aid in providing recommendations in this setting.

# Follow up protocol for Low Risk Disease

- . Physical examination, urine cytology (only for high-grade lesions), and cystoscopy

  - Every 3 months-first year
     Every 6 months thereafter-years 2 through 3
  - · Yearly-thereafter
- Contralateral imaging (IVU or retrograde pyelography)

  –yearly
- Ipsilateral endoscopy (patients undergoing organ-sparing therapy)

   Every 6 months-first several years

  - · Yearly-thereafter

# Follow up protocol for High Risk Disease

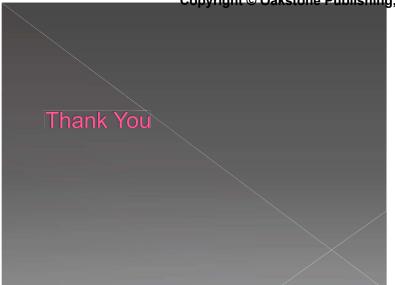
- Metastatic evaluation-necessary in all patients with significant risk of disease progression (i.e., high grade or invasive disease)
  • Physical examination, chest x-ray, comprehensive metabolic
  - panel with liver enzymes
    - · Every 3 months-first year
    - Every 6 months—years 2 through 3
       Yearly—years 4 and 5

    - · After 5 years-evaluation of urothelium only
  - Computed tomography or MRI of abdomen and pelvis-
    - · Every 6 months-years 1 and 2
    - · Yearly-years 3 through 5
  - · Bone scan-only for elevated alkaline phosphatase level or symptoms of bone pain

# Treatment of Metastatic Disease

- When there is evidence of regional lymph node metastases, initial chemotherapy should be given as the primary therapy, and surgery should be withheld until a good—ideally a complete—radiographic response is seen. At that time, consolidative surgery can be offered.
- Paclitaxel, cisplatin, and gemcitabine (PCG) versus gemcitabine and cisplatin (GC)- Bettter survival with addition of paclitaxel
- Carboplatin is frequently substituted for cisplatin because of either limitations of renal function or concerns over toxicity with the latter, but the results with carboplatin remain inferior.
- Upcoming molecule- Cabozantinib, the inhibitor of MET and VEGF pathways

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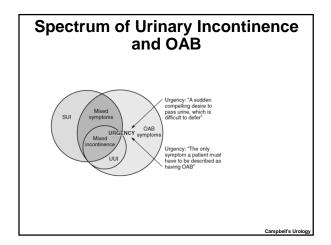
# Evaluation and Medical Management of OAB and Urinary Incontinence

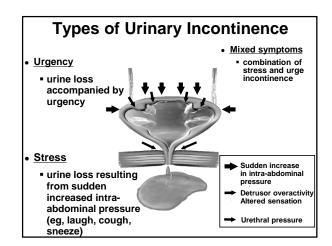
Gary E. Lemack, M.D.
Professor and Residency Program Director
UT Southwestern Department of Urology

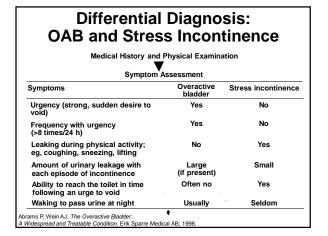


# **Disclosures**

 Consultant for Allergan, Astellas, Avadel, GTx, Urovant, Blue Wind







# Evaluation – Stress Urinary Incontinence AUA/SUFU Guidelines Statements 1-3

# PATIENT EVALUATION: GOALS

- Confirm SUI
- · Optimally characterize incontinence
- · Assess differential diagnosis
- Consider impact of coexisting conditions
- · Aid in treatment selection
- · Determine prognosis

# PATIENT EVALUATION

- 1. In the initial evaluation of patients with stress urinary incontinence desiring to undergo surgical intervention, physicians should include the following components: (Clinical Principle)
- · Focused history, including assessment of bother
- Focused physical examination, including a pelvic examination
- Objective demonstration of stress urinary incontinence with a comfortably full bladder (any method)
- Assessment of post-void residual urine (any method)
- Urinalysis

# PATIENT EVALUATION

The history, bladder diary, questionnaires, and/or pad testing should yield:

# PATIENT EVALUATION

Physical examination of SUI patients should include:

- Focused abdominal examination
- Evaluation of urethral mobility (any method)
- Supine and/or standing stress test with comfortably full bladder
- Assessment of pelvic prolapse (any method)
- · Assessment of vaginal atrophy/estrogenization status
- Focused neurologic examination

Diagnostic evaluation should include:

- Urinalysis
- PVR

# PATIENT EVALUATION

- 2. Physicians should perform additional evaluations in patients being considered for surgical intervention who have the following conditions: (Expert Opinion)
  - Inability to make definitive diagnosis based on symptoms and initial evaluation
  - Inability to demonstrate stress urinary incontinence
  - Known or suspected neurogenic lower urinary tract dysfunction
  - Abnormal urinalysis, such as unexplained hematuria or pyuria
  - Urgency-predominant mixed urinary incontinence
  - Elevated post-void residual per clinician judgment
  - High grade pelvic organ prolapse (POP-Q stage 3 or higher) if SUI not demonstrated with pelvic organ prolapse reduction
  - Evidence of significant voiding dysfunction

# PATIENT EVALUATION

- 3. Physicians may perform additional evaluations in patients with the following conditions: (Expert Opinion)
  - Concomitant overactive bladder symptoms
  - · Failure of prior anti-incontinence surgery
  - Prior pelvic prolapse surgery

# **CYSTOSCOPY & URODYNAMICS**

**Guidelines Statements 4-6** 

# CYSTOSCOPY & URODYNAMICS TESTING

- 4. Physicians should not perform cystoscopy in index patients for the evaluation of stress urinary incontinence unless there is a concern for urinary tract abnormalities. (Clinical Principle)
- 5. Physicians may omit urodynamic testing for the index patient desiring treatment when stress urinary incontinence is clearly demonstrated. (Conditional Recommendation; Evidence Level: Grade B)

# **CYSTOSCOPY & URODYNAMICS TESTING**

Diagnosis	After Office	Evaluation	P Value	After Urodynamic Testing (N = 294)†	P Value:
	Urodynamic- Testing Group (N=315)	Evaluation- Only Group (N=315)			
Stress urinary incontinence — no. (%)	315 (100)	315 (100)	>0.99	292 (99.3)	NA
Overactive bladder with incontinence — no. (%)	131 (41.6)	108 (34.3)	0.06	74 (25.2)	< 0.001
Overactive bladder without incontinence — no. (%)	99 (31.4)	94 (29.8)	0.67	61 (20.7)	0.002
Voiding dysfunction — no. (%)	7 (2.2)	9 (2.9)	0.61	35 (11.9)	< 0.001
Suspected intrinsic sphincter deficiency — no./ total no. (%) (	61/314 (19.4)	54/315 (17.1)	0.46	37/294 (12.6)	0.003

Nager 2012

# **CYSTOSCOPY & URODYNAMICS TESTING**

6. Physicians may perform urodynamic testing in non-index patients. (Expert Opinion)

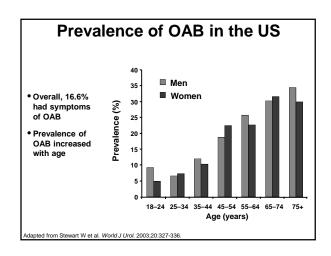
Urodynamic testing may be performed at the urologist's discretion in certain non-index patients to facilitate diagnosis, treatment planning, and counseling:

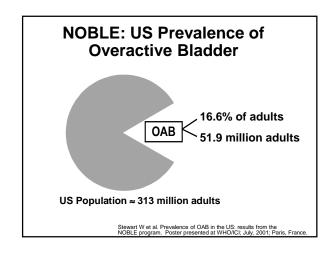
**Overactive Bladder and Urgency Incontinence** 

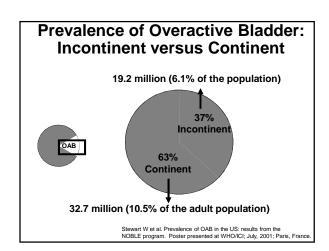
# **National Overactive Bladder Evaluation (NOBLE) Program**

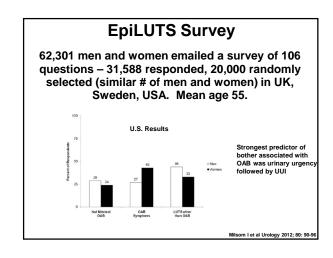
- Large US prevalence study for OAB
  - November 2000-January 2001
  - 17,231 households contacted
  - 5,204 completed interviews
  - 4,160 controls, 1,044 cases
- Conclusions
  - Over 33 million OAB sufferers (16.6% of population)
  - 63% OAB dry; 37% OAB wet
  - OAB significantly impairs health related quality of life, even in those without urge incontinence

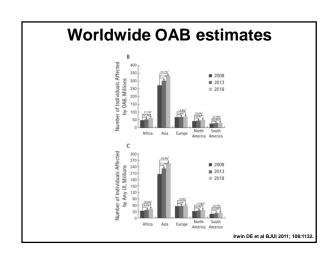
dapted from Stewart WF et al. World J Urol. 2003;20:327-336

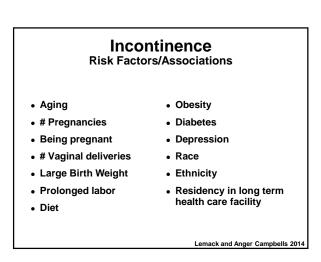


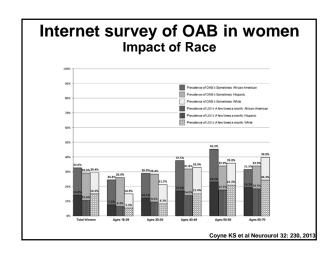


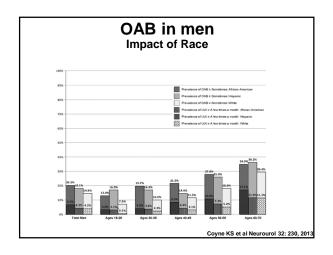


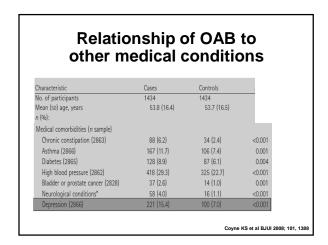




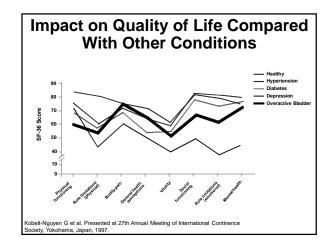


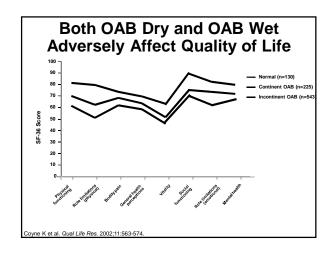






Impact of OAB on QOL

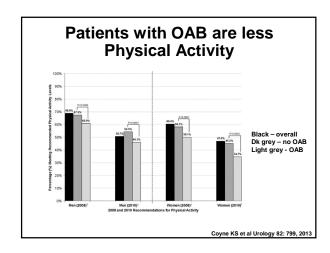




# **OAB** diminishes Quantity and **Quality of Sex**

- Survey of over 14000 men and women comparing those with OAB to those with no LUTS
- · OAB was strongest predictor of diminished sexual activity and significantly less enjoyment of sex (p<.00001)
- . Interestingly, being from Sweden (vs US), having IC, Neuro condition, Younger age, depression and anxiety ALL associated with less sex.
- · OAB also predictor of ED in men

Coyne KS et al J Sex Med 8: 1603, 2011



### Impact of OAB on Quality of Life Physical **Psychological** Limitations or cessation of Guilt/depression physical activities Loss of self-esteem Sexual being a burden Avoidance of sexual contact and intimacy lack of bladder **Quality of** urine odor Life Occupational Absence from work Social Decreased productivity •Reduction in social interaction Limiting and planning travel around toilet accessibility Requirements for specialized underwear, bedding Special precautions with clothing

Making a diagnosis of OAB

# Diagnosis of OAB

- · A presumptive diagnosis of OAB can be based on
  - patient history, symptom assessment
  - physical examination
  - Urinalysis → if positive MUST initiate workup
- Initiation of noninvasive treatment may not require an extensive further workup

Gormley EA et al J Urol 188: 2455, 201

# Other causes of OAB symptoms

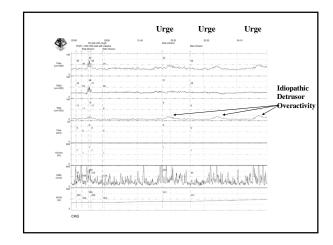
A shortened list...

- Pelvic Organ Prolapse
- Interstitial Cystitis
- Urinary tract infection
- Carcinoma in situ
- · Bladder outlet obstruction
- Polyuria
- Sleep disturbances
- Medication induced

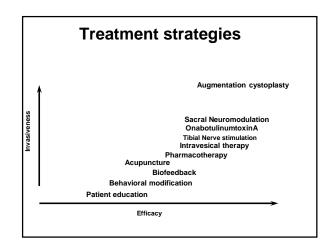
IF any of these diagnoses are suspected then additional workup is suggested

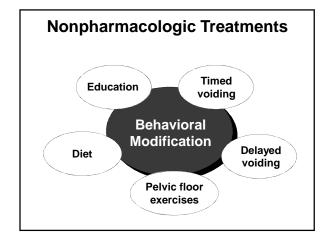
# What other testing – BE SELECTIVE

- Post void residual
- Urinary flow rate
- Cystoscopy
- Upper urinary tract imaging
- Lower urinary tract imaging
- Urodynamic testing



Management of OAB







# **Combined Behavioral and Drug Therapy for Urge Incontinence**

"Whether drug and behavioral therapy are combined from the onset or used sequentially in a stepped program, the evidence from the present study is that two interventions combined have a greater potential to enhance outcome than could be achieved by either intervention alone."

Burgio K et al. J Am Geriatr Soc. 2000;48:370-374

# **Diet Modification**

- · Daily fluid intake
  - reduce nighttime fluids to manage nocturia
- Eliminate bladder irritants such as:
  - caffeine
  - alcohol
  - nicotine
- Evaluate and modify bowel habits as appropriate
  - add fiber to diet

# **Behavior Modification**

- When the urge strikes:
  - Stop and stay still
  - Squeeze pelvic floor muscles
  - Relax rest of body
  - Concentrate on suppressing urge
  - Wait until the urge subsides
  - Walk to bathroom at normal pace

# Other therapies

- Vaginal estrogen
  - Proven efficacy in reducing recurrent UTI's in postmenopausal females
  - Appropriate for symptoms related to atrophic vaginitis
  - NOT consistently shown to have benefit for OAB (may worsen LUTS)

# **Antimuscarinic Agents**

- Tolterodine (Detrol® LA)
- Oxybutynin (Ditropan XL®, Gelnique®)
- Trospium (Sanctura®)
- Solifenacin (Vesicare®)
- Darifenacin (Enablex®)
- Fesoterodine (Toviaz®)

# Oxybutynin Ditropan

- Available for over 35 years
- . Initially prescribed for GI related effects
- · No agent has superior efficacy
- Side effect profile may be more pronounced
  - Cognitive dysfunction in frail/vulnerable
  - Constipation an issue in those on multiple meds

# Trospium Chloride

- Quarternary amine
  - All others tertiary amines
  - May impact ability to cross blood brain barrier
- Equal affinity for M2 and M3 receptors
- . Minimally metabolized by CYP450 system
- 60% of drug excreted in urine minimally metabolized

# Solifenacin succinate

Vesicare

- Competitive muscarinic receptor antagonist
- No food effect
- Highly (~98%) bound to plasma protein (α<sub>1</sub>-acid glycoprotein)
  - No significant drug-drug interactions with digoxin
- Metabolized (primarily by CYP3A4) in the liver
  - Alternate metabolic pathways exist
  - No significant drug-drug interactions with warfarin or oral contraceptives
- t<sub>1/2</sub> of ~50 hours (range 45-68)

# Darifenacin Enablex

- M3 selective muscarinic receptor antagonist
- Metabolized primarily by P450 enzymes
  - CYP2D6
  - CYP 3A4
- · No dose adjustment for renal insufficiency
- . Dose adjust for moderate hepatic impairment
  - Don't exceed 7.5 mg

# Fesoterodine Toviaz

- . Structurally related to tolterodine
- Parent compound has no affinity to muscarinic receptor
- Metabolized immediately by serum esterases
- Serum levels predictable (moreso than tolterodine), allowing dose increases. No "poor metablizers"
- Dose adjustments for severe renal/liver impairment.

# **Antimuscarinics**

Oxybutynin	Ditropan <sup>®</sup>	IR: 2.5 mg; 5 mg	Oral (tds)	1975
	Ditropan XL®	ER: 5 mg; 10 mg	Oral (qd)	1999
	Oxytrol	36 mg/patch (3.9 mg/d)	Transdermal	2008
	Gelnique	10% gel	Transdermal	2009
Tolterodine	Detrol <sup>®</sup>	IR: 1 mg; 2 mg	Oral (qd)	1998
	Detrol LA®	ER: 2 mg; 4 mg	Oral (qd)	2001
Trospium	Sanctura ®	20 mg	Oral (qd)	2004
Solifenacin	Vesicare ®	5 mg; 10 mg	Oral (qd)	2005
Darifenacin	Enablex ®	7.5 mg; 15 mg	Oral (qd)	2005
Propiverine	Detrunorm	15 mg	Oral (qd)	2006
Fesoterodine	Toviaz™	4 mg; 8 mg	Oral (qd)	2009

# **Antimuscarinics: Efficacy**

- A meta-analysis of the effects of antimuscarinics in OAB has confirmed:
  - · Antimuscarinics are efficacious
  - Greater proportions of patients treated with antimuscarinics than with placebo returned to continence
  - Antimuscarinics were more effective than placebo for mean change in the:
    - Number of incontinence episodes per day
    - Number of micturitions per day
    - · Number of urgency episodes per day
    - Volume voided per micturition
  - Profiles of each drug and dosage differ

Chapple C, et al. Eur Urol. 2008;54:543-56

# **Antimuscarinics: Tolerability**

- In a meta-analysis:
  - Dry mouth is the most commonly reported adverse event (29.6% on treatment vs 7.9% on placebo), followed by pruritus (15.4% on treatment vs 5.2% on placebo), constipation, headache and abnormal vision
- . Tolerability may limit persistence
  - Studies have shown that 6-month cumulative discontinuation rate for antimuscarinics in women is high at 59%
  - The median time to discontinuation of antimuscarinics in that study was 4.76 months

Chapple C, et al. Eur Urol. 2008;54:543-56

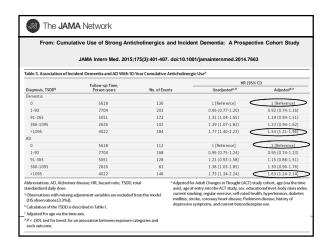
### Cumulative Use of Strong Anticholinergics and Incident Dementia

A Prospective Cohort Study

Shelly L. Gray, PharmD, MS; Melissa L. Anderson, MS; Sascha Dublin, MD, PhD; Joseph T. Hanlon, PharmD, MS; Rebecca Hubbard, PhD: Rod Walker, MS; Onchee Yu, MS; Paul K, Crane, MD, MPH; Eric B, Larson, MD, MPH

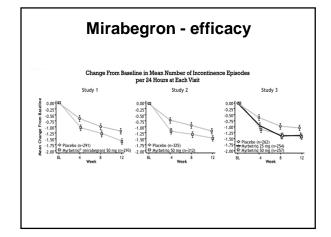
- · Prospective study
- · 3434 participant (1994-1996, 2000-2003)
- · 65 years old with no dementia at entry
- Computerized pharmacy dispensing data to calculate total standardized daily dose of anticholinergics (TSDDs) in the past 10 years
- Most recent 12 month data excluded to avoid possibility of acute mental status changes

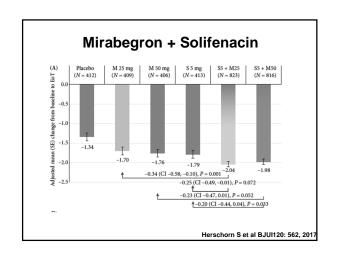
JAMA Intern Med. 2015:175(3):401-407.



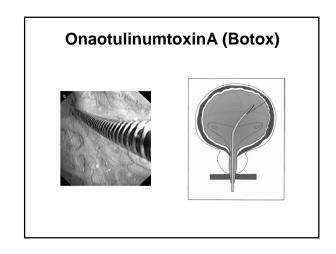
# Mirabegron Myrbetriq

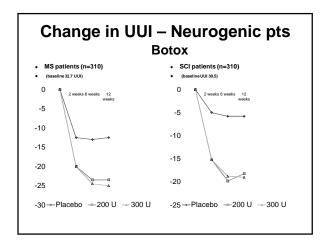
- Beta-3 agonist
- Once daily dosing 25, 50 mg
- . Minimal anticholinergic type side effects
- HTN closely assessed, minimal impact seen
- Avoid in those with poorly controlled HTN
- Efficacy similar to anti-muscarinic agents
- May be preferable in patients with heavy anticholinergic load

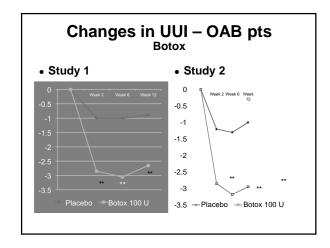




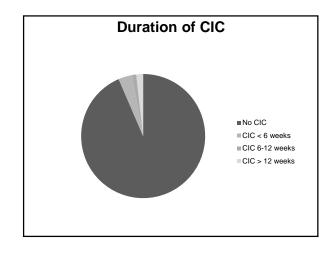
# Refractory OAB: What to do if medications fail?

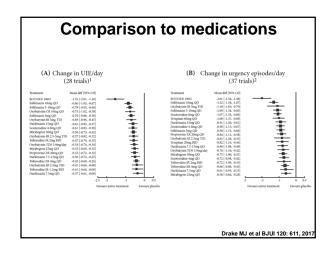


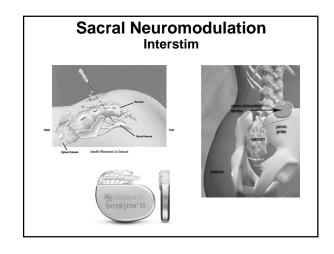


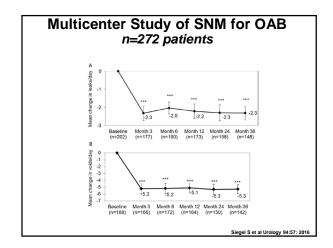


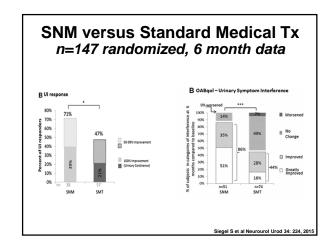
Adverse event	F	rst 12 wk	Entire treatment cycle		
	Placebo, n = 270	OnabotA 100 U, n = 274	Placebo, n = 270	OnabotA 100 U, n = 27-	
AEs with incidence > 3%, no. ()	K)				
UTI	14 (5.2)	56 (20.4)	26 (9.6)	66 (24.1)	
Dysuria	10 (3.7)	16 (5.8)	11 (4,1)	16 (5.8)	
Racteriuria	6 (2.2)	10(3.6)	9 (3 3)	17 (6.2)	
Urinary retention	1 (0.4)	16 (5.8)	1 (0.4)	16 (5.8)	
Haematuria	1 (0.4)	10 (3.6)	2 (0.7)	10 (3.6)	
Leukocyturia	2 (0.7)	7 (2.6)	2 (0.7)	10 (3.6)	
Residual urine volume	1 (0.4)	8 (2.9)	2 (0.7)	9 (3.3)	
Discontinuations, no. (%)	15 (5.6)	9 (3.3)	23 (8.5)	18 (6.6)	
Due to AEs	2 (0.7)	2 (0.7)	2 (0.7)	4 (1.5)	



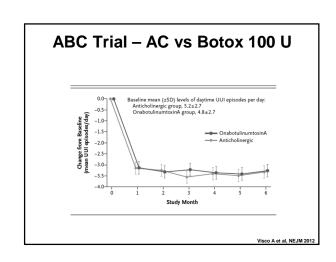


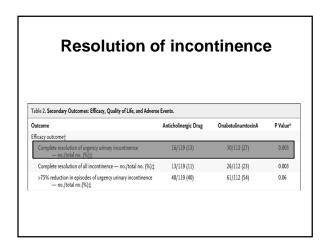


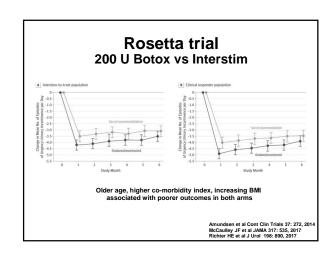


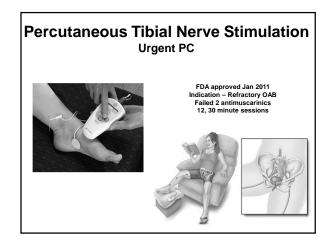


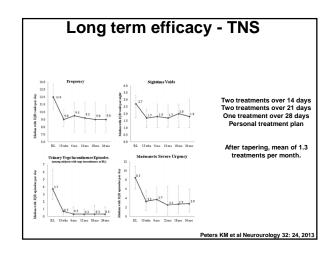
**Important Comparator Trials** 

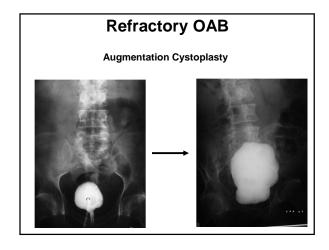


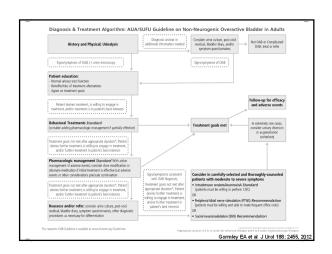


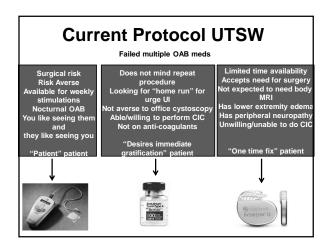


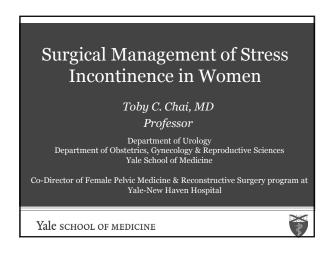


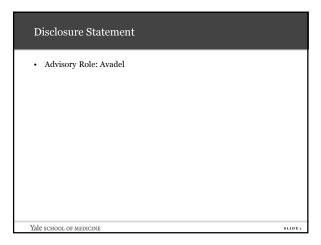












## Objectives of Talk

- Evaluation of SUI (Stress Urinary Incontinence) in the index women (no prior SUI surgeries, non-neurogenic, no co-morbidities that might affect bladder function)
- · Surgical options for SUI in index women
  - Urethral bulking agent
  - Mesh midurethral sling
  - Autologous fascial sling
- Complications from mesh midurethral slings
- · Surgical options for SUI in complex women
  - Prior SUI surgery

Yale school of medicine

# What is the International Continence Society (ICS) definition of SUI?

Complaint of involuntary leakage on effort or exertion or on sneezing or coughing

Yale school of medicine

SLIDE 3

# AUA/SUFU Guideline for Female SUI — 2017 Update Female Stress Urinary Incontinence: AUA/SUFU Evaluation and Treatment Algorithm EVALUATION (INDICATIONS) Initial evaluation The initial evaluation The initial evaluation of patients desiring to undergo surgical intervention should include the following components: Physical exam Demonstration of SUI Urinallysis Urinallysis Cystoscopy Should not be performed unless there is a concern for lower uniform year that chomonisalies Urodynamics May be omitted when SUI is clearly demonstrated Vale SCHOOL OF MEDICINE SELDE 4 Vale SCHOOL OF MEDICINE

# Other associated history points that are important – all related to pelvic floor issues

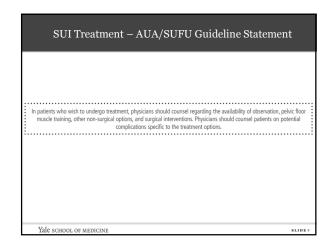
- Lower urinary tract symptoms (frequency, nocturia, hesitancy, straining, etc.)
- Pelvic organ prolapse symptoms and bother (feeling of bulge in vagina, seeing something coming out, feeling of pressure in vagina)
- Fecal motility symptoms and bother (constipation, fecal incontinence)

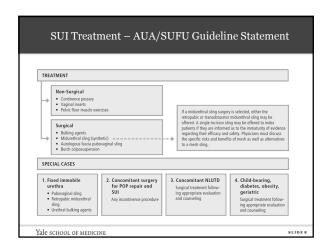
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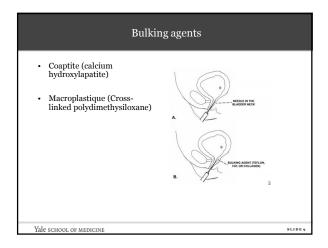
SLIDE 5

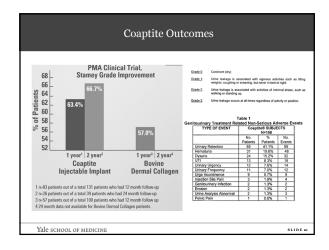
# Copyright © Oakstone Publishing, LLC, 2018. All Rights Reserved.

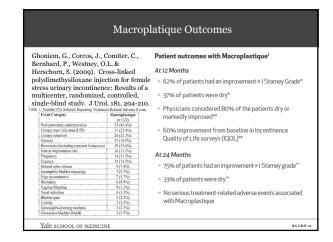
# Decision to treat patient is not based just on having UI symptom • <u>degree of bother</u> and impact of UI on patient's <u>quality of life</u> (QoL) from the UI





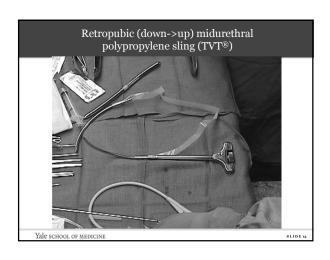


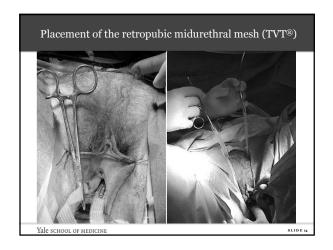




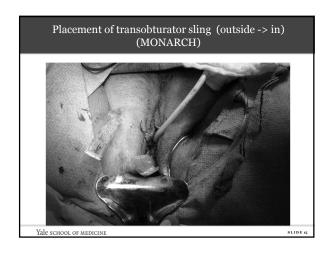
# Copyright © Oakstone Publishing, LLC, 2018. All Rights Reserved.

# Mid-Urethral Polypropylene Slings • Retropubic (e.g. TVT) -up->down -down->up • Transobturator -Inside->out (TVT-O) -Outside->in (MONARCH)

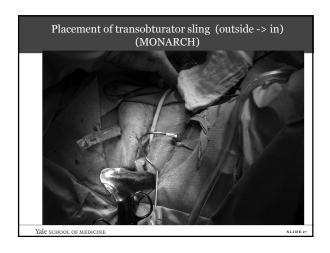




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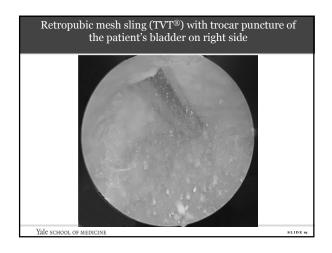


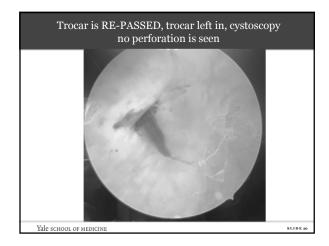


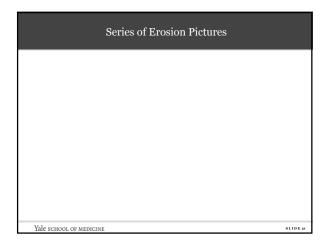
# Complications of midurethral slings

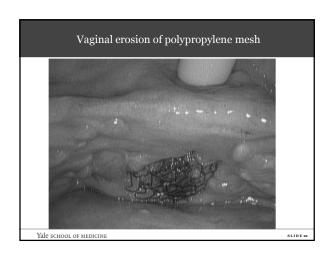
- · Bladder perforation
- Injury to major blood vessels, bowel during trocar pass intraop (retropubic approach)
- · Recurrent urinary tract infections
- Urinary retention
- De novo overactive bladder symptoms
- Pelvic pain / thigh pain / dyspareunia
- Erosion of mesh into vagina, bladder, urethra, bowel in the post-operative period at any time

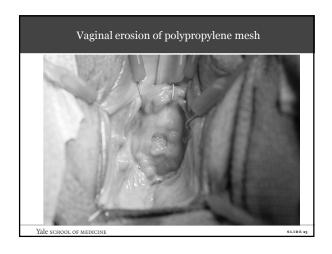
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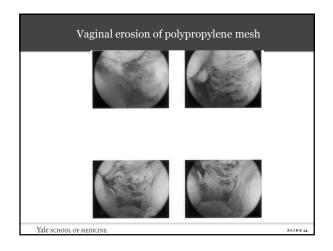


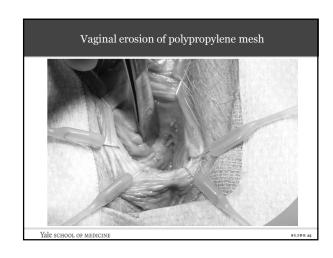


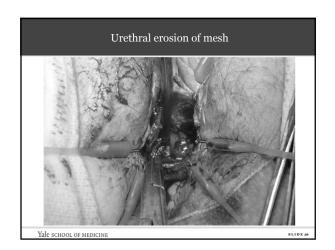


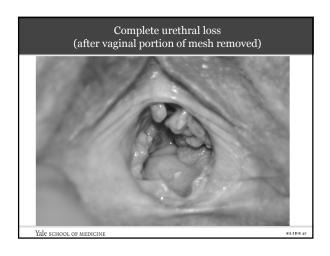


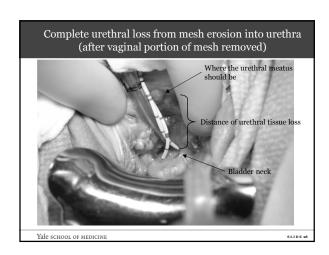
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# My editorial about 2 papers published in Sept 2017 *Journal of Urology* about mesh removal

What are the takeaway messages from these papers? Although mesh slings are considered the gold standard procedure, complications requiring removal still develop. As presented in these 2 reports, slings were removed 3 to 6 years after implantation. Mr. Therefore, long-term followup of patients who receive mesh slings is paramount and probably should be indefinite. Since de novo stress incontinence developed between 10% and 20% of the time, this means that it is more likely that a woman will remain stress continent than become stress incontinent after mesh sling removal. This is something that we can tell our patients who are facing mesh sling removal.

Although the complications of neutial much aling

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CIIDE --

# Which midurethral sling is better – retropubic or transobturator?

- Some data suggest retropubic is better than transobturator, especially for low VLPP (Valsalva leak point pressure) and low MUCP (maximum urethral closure pressure) situations
- Risks for retropubic versus transobturator slightly different (increased bladder and bowel perforation risk with retropubic, increased thigh/leg pain risk with transobturator)

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CLIDE -

# TOMUS Trial: TVT versus TVT-O/MONARCH RCT n=~600 (~300 TVT and ~300 TVT-O)

The NEW ENGLAND JOURNAL of MEDICINI

ORIGINAL ARTICLE

### Retropubic versus Transobturator Midurethral Slings for Stress Incontinence

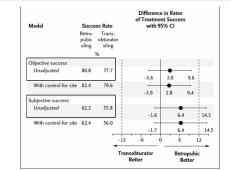
Holly E, Richter, Ph.D., M.D., Michael E, Albo, M.D., Halina M. Zyczynski, M.D., klimberly Kenton, M.D., Peggr A, Norton, M.D., Larry T, Siris, M.D., Stephen R, Kruss, M.D., Toly, C. Chai, M.D., Gary E, Lemack, M.D., Kimberly J, Candreo, M.S., R. Edward Varner, M.D., Shaw Menefee, M.D., Chiar G, Chetti, M.D., Linda Brubaker, M.D., Ingeld Nyagand, M.D., Salli Khandwala, M.D., Thomas A, Rozanski, M.D., Harry Johnson, M.D., Joseph Schaffer, M.D., Anne M. Stoddard, S.D., Robert L. Holley, M.D., Charles W, Nager, M.D., Pamela Moalli, M.D., Ph.D., Elizabeth Mueller, M.D., Army M. Arisco, M.D., Marlene Corton, M.D., Sharon Tennstett, Ph.D., T. Debuene Chang, M.D., E. Ann Gormley, M.D., and Heather J. Liman, Ph.D., T. Debuene Chang, M.D., E. Ann Gormley, M.D., and Heather J. Liman, Ph.D., The University of the Univary Incontinence Teatment Network\*

N Engl J Med. 2010 Jun 3;362(22):2066-76.

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SLIDE

# Trial Design was a EQUIVALENCE trial with 12 months post-op as primary outcome timepoint Difference in Rates of Treatment Success With 95% CI



SLID

# Composite Outcome Assessment

- · Objective criteria for success
  - Negative cough stress test
  - Negative 24-hour pad test
  - $\,-\,$  No retreatment for SUI (behavioral, pharmacologic or surgical treatment for SUI)
- Subjective criteria for success
  - Absence of self-reported symptoms of SUI using validated PRO instrument
  - No leakage recorded on a 3-day voding diary
  - No retreatment fro SUI

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LIDE 34

# TOMUS Trial: 24 months data

### Treatment Success of Retropubic and Transobturator Mid Urethral Slings at 24 Months

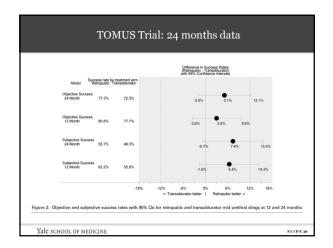
Michael E. Albo, \*,† Heather J. Litman,‡ Holly E. Richter, \$ Gary E. Lemack,||
Larry T. Sirls,‡ Toby C. Chai,¶ Peggy Norton,‡ Stephen R. Kraus,\*\*
Halina Zyczynski,†† Kimberly Kenton,‡ E. Ann Gormley‡‡ and John W. Kusek‡ for
the Urinary Incontinence Treatment Network

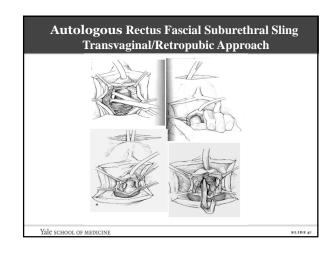
From the University of Culfornia, Son Diago, La Jolla, Culfornia MEGIA, New Expland Research Institutes, Watersone, Massachusette #ULL University of Hassac Submesters (Palla III), University of Hassac Submesters (Dalla III Cillia University of Hassac Submesters (Dalla III Cillia III Ci

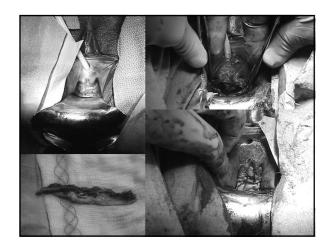
 ${\it Journal of Urology~2012~Dec;} 188 (6): 2281\text{-}7.$ 

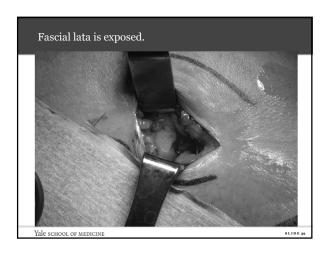
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SLIDE 35

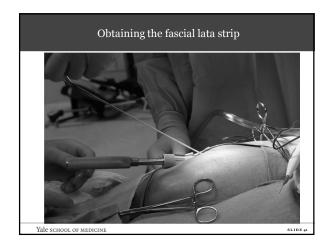














## What do we do next when a patient fails a mesh sling?

First, let's define what might comprise "failure"

- · Urinary retention
- · Recurrent UTI
- Altered patterns of voiding (bending, straining, hesitancy)
- De novo overactive bladder symptoms / urgency urinary incontinence
- · Recurrent stress urinary incontinence
- · Mixed urinary incontinence
- · Dyspareunia

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crine.

## Sling complication considerations

- If bothersome symptoms such as urinary retention, incomplete bladder emptying, difficult voiding, straining/hesitancy to void occur immediately after sling surgery, cut sling without any other texts.
- De novo OAB symptoms may represent idiopathic cause or response to bladder outlet obstruction. Consider doing urodynamics for de novo OAB to help clarify whether bladder outlet obstruction is present in which case, cutting sling may resolve OAB symptoms.
- Recurrent UTI can be a harbinger to erosion of sling into urinary tract (bladder, urethra) and formation of stone on . Patient may also have outlet obstruction as cuase for recurrent UTI.

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SLIDE 44

SLIDE 4

# What happens to bladder outlet after a sling? urodynamics pre- and post- sling

Female Urology

Urodynamic Changes Associated with Successful Stress Urinary Incontinence Surgery: Is a Little Tension a Good Thing?

Stephen R. Kraus, Gary E. Lemack, Larry T. Sirls, Toby C. Chai, Linda Brubaker, Michael Albo, Wendy W. Leng, L. Keith Lloyd, Peggy Norton, and Heather J. Litman, for the Urinary Incontinence Treatment Network\*

Urology. 2011 Dec;78(6):1257-62.

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### CHANGE in UDS for autologous slings -Post minus Pre Values Success Failure Sling Sling P Values Mean (SD) Mean (SD) Success vs Failure -3.8 (13.8) -33.5 (157.8) 8.0 (56.3) -42.1 (152.4) -37.52 (230.5) NIF Q<sub>max.</sub> NIF volume NIF PVR -5.0 (12.5) 13.0 (192.4) 84 84 84 96 71 .58 .26 .29 .09 11.1 (61.65) 4.5 (130.14) MCC Compliance PFS Q<sub>max</sub> 5.8 (241.4)

# What to do next after patient fails a sling with recurrent SUI?

Curr Urol Rep (2014) 15:427 DOI 10.1007/s11934-014-0427-

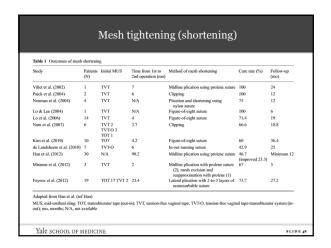
FEMALE UROLOGY (K KOBASHI, SECTION EDITOR)

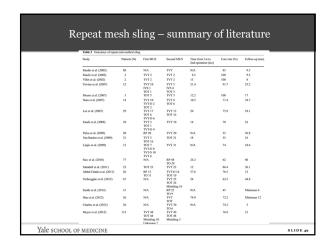
### Management of Recurrent Stress Incontinence Following a Sling

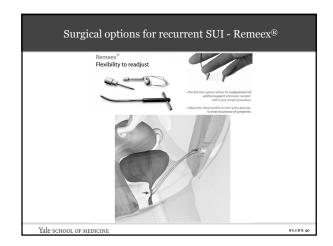
Geneviève Nadeau • Sender Herschorn

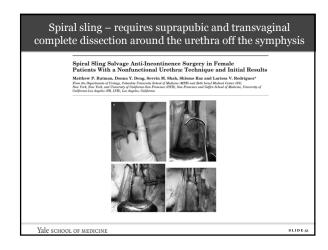
- · Tightening of implanted sling
- · Repeat midurethral sling
- Bladder neck sling
- Autologous fascial sling (rectus fascia, fascia lata)
- · Spiral sling
- · Re-adjustable sling (Remeex®)
- · Adjustable continence therapy
- · Artificial urinary sphincter
- Urinary diversion

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Does baseline (pre-sling surgery) urodynamics predict post-sling success/failure

Baseline Urodynamic Predictors of Treatment Failure 1 Year After Mid Urethral Sling Surgery

Charles W. Nager,\*, t Larry Sirls,† Heather J. Litman,† Holly Richter,‡ Ingrid Nygaard,† Toby Chai,§ Stephen Kraus, Halina Zyczynski,¶ Kim Kenton,\*\* Liyuan Huang,† John Kusek† and Gary Lemack†† for the Urinary Incontinence Treatment Network

From the Department of Reproductive Medicine, University of California Sim Diago, San Diago, California (CMR), Department of Linkogy, William Bisuamont Hospita, Ripard Lak, Merkipar LS, New England Research Institute, Wilsterbown, Massachaette 8/LL, Ut. Department of Clostetics and Opposition, Visional Policy, University of Olds, Diabette and Digentive and Kehry Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Olds, Diabette and Digentive and Kehry Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Olds, Diabette and Digentive and Kehry Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Olds, Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Olds, Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Olds, Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Olds, Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Olds, Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Olds, Diseases, Betheads (SQ, Marjant, Department of Linkogy, University of Diseases, Sanca, Mages Violence, San

Does baseline (pre-sing surgery) urodynamics predict
post-sling success/failure

• Low VLPP
• Low MUCP

# Conclusions

- Surgical approaches can be used effectively to ameliorate SUI
- However, selection of patients is important.
   Properly selected and counseled patients will have the best outcomes
- Shared decision making is a key component of patient- centered health care. It is a process in which clinicians and patients work together to make decisions and select tests, treatments and care plans based on clinical evidence that balances risks and expected outcomes with patient preferences and values

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LIDE 54

# MANAGEMENT OF SPHINCTERIC URINARY **INCONTINENCE IN MEN AFTER RADICAL PROSTATECTOMY**

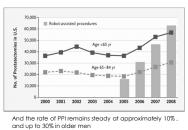
Craig V. Comiter, MD

Professor, Urology Stanford University Medical School

## **DISCLOSURE STATEMENT**

Nothing to disclose

# PPI IS BECOMING MORE COMMON... BECAUSE OF THE ROBOT



- 200,000 cases of prostate cancer per year in US
  - · 40% will choose RRP for treatment
- Not all men who leak will elect further treatment
  - 6%-9% with enough bother for surgery for PPI
  - Stanford JL, JAMA 2000, 283:354-360. Litwin MS. J Urol 2000, 164:1973-1977. Kundu SD, J Urol 2004, 172:2227-2231 2-5% (American – Canadian) will opt for surgery

# **RISK FACTORS**

- Pre-operative continence status
- And voiding dysfunction
- Tumor stage
- Age at time of surgery
- Functional urethral length
- Previous XRT
- Obesity

# PRE-OP INCONTINENCE

- US adults 5.4% with incontinence
  - 26% of those with isolated SUI (1.3% background SUI)
  - Highest risk for PPI
    - Baseline ISD
- Pre-op bladder dysfunction adversely affects post-op continence
  - Neurogenic DO
  - Pre-op BPO
    - DO, DUA, myogenic insult

# STAGE / SURGICAL APPROACH

- Poor correlation between stage and incontinence
  - But stage may affect approach Loeb S. Urology. 2007; 69:1170-1175.
- Nerve sparing
  - No difference (Lepor H. J Urol 2004; 171:1216)
  - Beneficial effect of bilateral nerve sparing (Nandipati KC, Urology)
- Bladder neck preservation
  - Improved continence at 3 months, no change by 6-12 months
- Robot/Lap vs Open RP
- Similar outcomes (Aherling TE, Urology 2004: 63:819)
- Perineal vs RP no difference (Young MD, J Urol 2003; 170:2374)

# **AGE**

- Advanced age as a risk factor Rogers CG, J Urol 2006; 176:2448-2452.
- vs delay in return to continence
- Lepor H, J Urol 2004; 171:1216-1219.
- Men age 70-74 3x more likely to undergo AUS for PPI compared to those age 45-49
  - Rogers CG, J Urol 2006; 176:2448-2452
- Progressive reduction in sphincter striated muscle cells with age
  - Young MD,. J Urol 2003; 170:2374-2378.

# PRE-OP FUNCTIONAL URETHRAL LENGTH

- Pre-op length of functional/membranous urethra
  - · related to PPI
- MRI
- If length > 12 mm, 89% continence
- If length < 12 mm, 77% continence
- UDS

Shorter functional urethral length predicts incontinence Strasser H. J Urol 1998: 159:100-104 Van Kampen M, Urol Int 1998; 60:80-84

# **OBESITY**

- BMI > 30 kg/m2

  - Higher risk of post-op complications
     Wound infections, anastomotic stricture, urinary incontinence
     Up to 3x risk of incontinence for obese vs non-obese
  - 25% of men with BMI > 30 kg/m2 with PPI Difficulty with urethral anastomosis, adverse medical factors
    - DM, vascular disease, HTN
      - Wolin KY, J Urol 2010; 183:629-633.

# XRT

- Salvage RP (after XRT)
  - Effective option in carefully
  - selected patients Increased risk of
  - complications • Rectal injury, anastomotic stricture, PPI
  - PPI in 25%-78%
  - Nearly 50% AUS rate after salvage RP
    - Sanderson KM. J Urol 2006:176:2025-2031

## **PATHOPHYSIOLOGY**

- Bladder vs Outlet
- Bladder
- DO, DUA, poor compliance
- Outlet
- ISD, BOO, ? Mobility
   Stricture, BOO overflow
- Consider pre-operative bladder dysfunction

# **BLADDER DYSFUNCTION**

- Pre-existing vs de novo
  - Denervation, obstruction
- Post -op impaired contractility, poor compliance
  - Previously thought to resolve by 8 months
  - Recent: ↓ compliance in 1/3, persists in 28% at 36 mos
  - Detrusor underactivity in ½, persists in 25% at 36 mos
- Persistent bladder dysfunction in significant minority even up to 3 years post-op

# **EVALUATION**

- History
   Pre-op continence, defecation
   Pharmacotherapy, other therapy
   XRT, TURP

- Physical exam
   GU tract, neuro-urological
   S2-S4 segments perineal sensation, PF contraction, BCR, DRE
- Urinalysis, PVR
- Freq, nocturia, inconfinence episodes, voided volume, 24-hr output

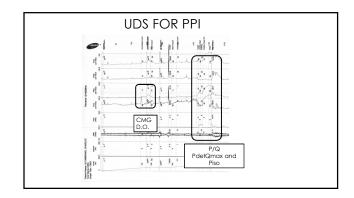
  Fluid intake, bladder capacity, freq of leakage

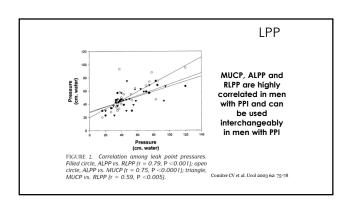
  4-day diany = to 7 day diany

  Fosters compliance
- Fosters compliance
   Va-thr home-based pad test
   More reproducible than 1-hour test
   24 hr pad test assist to perform, can be standardized.
   I hour test has its own advantages; no need for home test and water tight container
   Schick E, Neurourd Unayln 2003, 22:92-98.
   Mourisme L, Neurourd Unayln 1989, 3:79-507.

# INDICATIONS FOR URODYNAMICS

- Ask a question whose answer affects treatment algorithm or outcome
- Example: is there storage dysfunction? Bladder dysfunction?
- Post -op impaired contractility, poor compliance
- Is there SUI due to ISD? Or DO?
  - Or both?
- Is there BOO?
  - Could be answered with cystoscopy if there is a tight stricture
- Can the bladder contract adequately
  - To permit emptying after sling placement?
- If there is no question, then UDS is not indicated
   Or if the answer does not affect the outcome





# UDS – THE PUNCH-LINE ISD as sole cause in > 2/3 Isolated bladder dysfunction <10%</li> Sphincter and bladder dysfunction coexist in 1/3 Groutz A, J Urol 2000;163:1767–1770. Ficazzola MA, J Urol 1998;160:1317–1320.

# CHARACTERIZATION OF SUI CAN AFFECT DECISION

- Urethral mobility affects T-O sling outcome
  - Repositioning test
  - Rehder P, Arch Esp Urol 62:860, 2009
  - Residual sphincter function affects sling outcome
- Soljanik I, World J Urol 30:201, 2012
- LPP
  - Success of urethral bulking higher in those with higher LPP
  - < 60 cm water predicts failure</li>
     Sanchez-Ortiz RF, J Urol 158:2132, 1997
- Degree of urethral mobility varies in different patients
  - Comiter CV, et al, WSAUA, 2010

# OPTIMIZING PT SELECTION - REPOSITIONING TEST • Positive - (adequate coaptation) With elevation of the perineum by the examiner during urethroscopy, there is contraction of the EUS • Negative (poor coaptation)

# OPTIMIZING SLING RESULTS-SELECTING IDEAL PATIENT BASED UPON URODYNAMICS

- Rule out obstruction
  - BOO due to anastomatic stricture in 2.7%-20%
     Kundu SD, J Ural 2004, 172:2227-2231.
     Kao TC, J Ural 2000, 163:858-864.
- Assess for DO
  - D.O., low capacity adversely affects sling outcome
     Warner JN, Neuroural Urodyn 2012, 31:1124-7
     Crites MA, Urology 2011, 1:63.
- · Check contractility
  - Detrusor Underactivity (DUA) relative contraindication to sling
  - Potentially obstructive sling in pt with DUA poses risk of retention
     Sling is designed to prevent leakage with straining

  - Therefore interferes with/prevents voiding by Valsalva
     In large cohort of men with PPI, no instances of prolonged retention in men with normal contractility
    - Comiter CV. Neurourol Urodyn 2005: 24:648-653
  - Versus rates of 2% to 21% in cohorts without UDS

### DEFINING OUTCOME- DEFINING CONTINENCE

- Can only optimize if we can define/measure success
- Defining continence after RRP in the literature
  - Total control/perfect continence/dry
  - · Occasional leakage, no pad < 1 pad per day</p>
    - 1/3 to  $\frac{1}{2}$  of men who do not wear pads will have occasional leakage of urine

      - Wallerstedt A, et al. J Urol 187 196, 2012
         Rodriguez E et al, Urology 67: 785, 2006.
- HRQOL strongly correlates with level of leakage
   Wearing 1 pad (even if 'security' pad)

  - Negatively affects QOL vs wearing no pad at all
     Liss MA, et al: J Urol 183:1464, 2010

### SHOULD WE USE SIMILAR OUTCOME MEASURES AFTER SURGERY?

- Men are generally dry before RRP
  - · Thus wearing a pad after is a major deterioration
  - Very rarely are LUTS improved with RRP
- Men are always wet before PPI surgery
- Improvement is likely
   Worsening is unlikely
- Pad free or dry may be difficult (and unnecessary)
- HRQOL has not been shown to differ in men with and without 1 pad per day use following SUI surgery
- Set reasonable expectations -
- Pad free during non strenuous activities
   Need pad during straining

### WHAT OUTCOMES MEASURES ARE APPLICABLE AFTER PPI SURGERY?

- - Patient Global Impression of Improvement (PGI-I)
     Preferred subjective measure of success
     Worse, same, better, much better, very much better

    - Much better & very much better = success
       FDA, SUFU
- Objective · Pad weight

  - 24 hour pad test
     1 hour pad test (ICS)
  - Pad use
- · What is cure vs success vs failure?

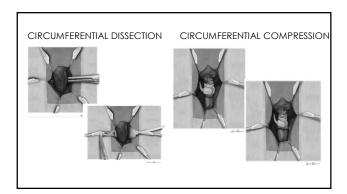
DEFINING SUCCESS - ACCORDING TO THE FDA (AT 12 MONTHS)

- Objective: change in 24-hour pad weight
   Cured: Dry, < 1.3 g on 24 hour pad test
   Very Much Improved: <12 gm or 90% reduction in pad weight

  - Much Improved: 50% 89% reduction of pad weight Improved: 25% 49% reduction of pad weight Failed: < 25% reduction of pad weight
- Subjective: PGI-I score post implant
   Very much better
- Much better
- Secondary endpoints:
   ICIQ and UCLA-RAND Inconfinence Index
   Change in pad use
   Device and procedure related adverse events



**AUS** 



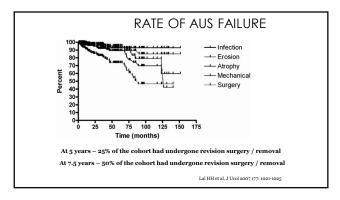
# **AUS** advantages

- Predictable success
  - Regardless of degree of SUI
- Best choice for XRT
- Best choice for revision surgery
- Long term data
- Minimal postoperative pain
- Detrusor overactivity
  - No adverse effect on outcome
  - Lai HH et al. Urol 2009, 73: 1264-1269
- Poor detrusor contractility

  - No adverse effect on outcome
     Lai HH et al. Urol 2009, 73: 1264-1269

# **AUS** disadvantages

- Pt need to manipulate pump
- Erosion rate
- Infection rate
- Revision rate
  - 21% at 5 years
  - 50% at 10 years
- Worry about catheterization



# **EARLY FAILURE**

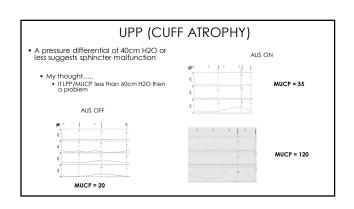
- Early (persistent incontinence)
  - Cuff is too large/loose
  - Improper reservoir pressure Device puncture / fluid leak
  - · Detrusor overactivity
  - Poor compliance
     Urinary retention

Ideally use a 4.0 to 4.5 cm cuff 61 - 70 cm H2O reservoir

# LATE FAILURE

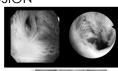
- Device malfunction
- Urethral Atrophy
- Urethral Erosion
- Detrusor Overactivity
- Decreased Bladder Compliance
- Inadvertent Device Inactivation

# **IMAGING** • Radiograph (if contrast used) Determine reservoir and pump filling Do both open and closed Theoretic risk of crystals with contrast if mixed improperly Examine for fluid in reservoir IF MISSING FLUID THIS SUGGESTS A LEAK However only 2cc of leak can lead to malfunction (HARD TO SEE)



# **URETHRAL EROSION**

- · Remove all hardware
- Attempt to repair urethra / capsule
- 16 F catheter for 3-4 weeks (16 F)
- Redo surgery 6-24 weeks later O Cystoscopy first to rule out stricture
  O New site O Transcorporal ?





## **URETHRAL ATROPHY**

- New site
- Transcorporal placement
- Downsize cuff
  - · 3.5 cm cuff now available
  - No increased risk of erosion compared to larger cuff<sup>1</sup>
- Double cuff
  - · Usually second more proximal
  - Need to increase fluid in reservoir by 2 or 3 cc's
  - Increased risk of complication compared to single cuff <sup>2</sup>
- · Urethral wrap
  - One small case series 5 of 8 patients failed <sup>3</sup>
- Increased reservoir pressure

Hudak SJ et al. J Urol 2011, 186: 1962-1966
 O'Connor RC et al. Urol 2008, 71: 90-93
 Trost L et al. Urol 2011, in press

### The good news is...

- 1 ppd rates 59-90%
- Pad free 10-72%
- Martins, Boyd, J Urol, 1995
   Litwiller, et al, J Urol, 1996
- Satisfaction rates 87-90%

  - Haab, et al: J Urol, 1997
    Lai, et al: J Urol, 2007
    Elliott Barrett, J Urol, 1998
- AUS most predictably successful surgery for PPI
- Largest body of literature with long term success

### The bad news is...

- Explantation 7-17%
  - Gousse, et al: J Urol, 2001
- Mechanical Failure +Urethral atrophy 8-45%
  - Lai, et al , J Urol, 2007

# SLING - MECHANISM OF ACTION

The principle of continence/urethral support is similar for all slings

- elevation and suspension of the pelvic floor muscles
- passive compression of the urethra
- Sustained sling tension is necessary for continence
- Over-correction with consequent urinary retention
- Under-correction with recurrent incontinence
- Balance of continence, adequate emptying, patient satisfaction.

## THE EVOLUTION OF THE SLING - NON ADJUSTABLE

- Transobturator Retroluminal Sling
  - · Relocates proximal urethra non compressive
  - Has minimized surgical invasiveness
- Perineal Bone Anchored Sling
  - Compresses perineal urethra
     Excellent fixation with bone anchors
- Quadratic Sling Relocate proximal urethra and compress perineal urethra











# QUADRATIC SLING - VIRTUE

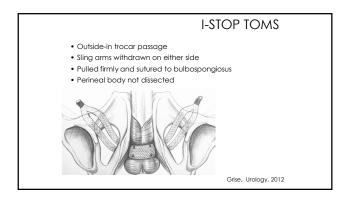
- 5.5 x 7 cm large pore monofilament polypropylene mesh
  - Inferior (trans-obturator, TO) extensions 1.5x 22.5 cm
     Superior (pre-pubic, PP) extensions 1.5 x 25 cm
- T-O component relocates proximal urethra
- P-P component broadly compresses perineal urethra
   Avoids bone anchors

  - Slippage of sling off bulbar urethra not possible
     Due to pre-public component
    Further evolution to "fixetion"
     Improved subjective (PGI-I ) and

  - objective (pad weight) results
     Prevents early loss of efficacy
  - - · Comiter, Urology, 2014



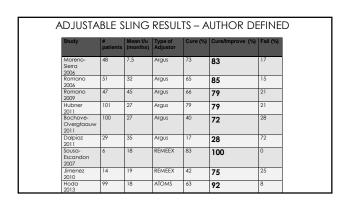
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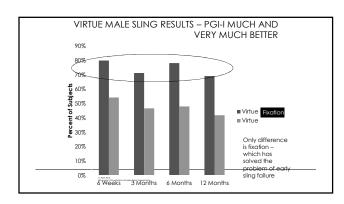




BONE	-AN	CHORE	ED SLIN	g res	ULTS - 24 N	1OS.
٨	ΛEΑI	N F/U –	AUTHO	R-DEF	FINED SUCC	CESS
Study	# pts	Mean f/u (months)	Sling material	Cure (%)	Cure/Improve (%)	Fail (%)
Ullrich 2004	36	25	Synthetic	67	92	8
Stern 2005	75	48	Synthetic	36	68	32
Rajpurkar 2005	46	24	Synthetic or organic	37	74	26
Comiter 2005	48	48	Synthetic	65	85	15
Migliari 2006	49	32	Synthetic	30	63	37
Fischer 2007	62	56	Synthetic	37	58	42
Giberti 2008	36	41	Synthetic or organic	62	70	30
Guimaraes 2009	62	28	Synthetic	65	88	12
Carmel (2009)	45	36	Synthetic	36	76	24
Athanasopoulos (2010)	43	24	Synthetic	51	81	19

Study	N	Mean f/u (months)	Cure (%)	Cure/Improve (%)	Fail (%)
Rehder (2010)	118	12	74	91	9
Grise (2011)	122	12	59	87	13
Bauer (2011)	126	27	52	75	25
Cornel (2010)	35	12	9	54	46
Cornu (2011)	136	21	62	78	22
Chaparro (2009)	20	24	65	65	35
Li (2012)	66	24	32	56	44
Grise (2012)	103	12	59	79	21
Rehder (2012)	156	36	42	77	23
Collado (2013)	61	26		80	20





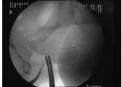
# RISK FACTORS FOR SLING FAILURE

- Historical Risks
  - Prior AUS
  - Prior urethral stricture
- Degree of Incontinence
- · Higher pad weight
  - > 200 g/24 hrs
    > 450 g/24 hrs
  - Higher pad use
- -Cornu JN, et al: BJUI 2010:108:236 -SoljanikI : World J Urol 2012 30:201 -Crites MA, et al: Urology 2011 -Fisher MC, J Urol, 2007 -Comiter, Curr Opin Urol, 2007, 2015
- Urodynamic Risks
  - Low MUCP Low ALPP
  - · Low functional urethral lenath
- Presence of DO
- Repositioning Test
- Weak residual sphincter function
   Incomplete closure of sphincter
- Surgical Technique
- Failure to tunnel sling
   Poor sling/suture fixation
- Surgeon inexperience
   Non-familiarity with new technique

### MAIN RISK FACTOR FOR FAILURE...

- Most of the aforementioned factors equate with worse ISD
  - History: severe leakage
    - XRT, brachytherapy, cryotherapy
  - Pad test: high volume
  - UDS: low MUCP, LPP
  - Negative repositioning test
- With suboptimal urethral compression

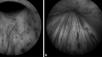
# OPTIMIZING PT SELECTION - URETHRAL REPOSITIONING TEST









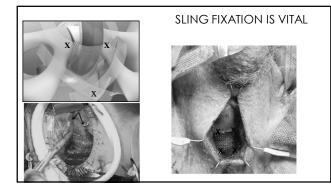


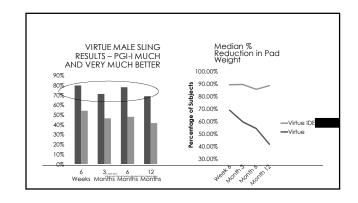


### OPTIMIZING RESULTS -**REPOSITIONING TEST - PROGNOSIS**

- Positive test: sphincter closes concentrically during repositioning

   Lengthening of zone of coaptation by > 1 cm
- Positive in 81.5% 83% cure/no pads
- Negative in 18.5%25% cure/no pads
- Correlates to Marshall test in women
- Urethral mobility affects T-O sling outcome





# EVALUATION OF PERSISTENT PPI FOLLOWING SLING

- History and Physical Exam
   Did original sling work temporarily?
   Timing of recurrent incontinence

  - Stress vs urge
     Demonstrate leakage during strain
- · Urodynamics
  - Only if there is a questions whose answer changes treatment
  - Bladder vs outlet leakage
  - Contractility
    - If considering a more compressive/quadratic or adjustable
  - Uroflow/PVR can rule out obstruction/incomplete emptying
- Cystoscopy
   If stricture is suspected
   If erosion is suspected



1. Harris et al Urology, 2008 (E pub)

# TREATMENT OPTIONS FOR RECURRENT INCONTINENCE AFTER SLING

- Periurethral bulking injection
- Place second transobturator sling
  - Remove sling
- Leave sling in situ
- Place quadratic sling
  - Remove sling Leave sling in situ
- Place adjustable sling
  - T-O or Retropubic
- Place artificial urinary sphincter
- Remove sling
   Leave sling in situ
- ProACT

## REPEAT T-O SLING FOR RECURRENT PPI

- 35 patients with mild-moderate SUI after failed first RTS
- After 6 months following repeat sling:

   45.5% (15 of 33 patients) no pad use
   30.3% (10 of 33 patients) 1 dry

  "security" pad

   3% (1 of 33 patients) 1 wet pad
   6.1% (2 of 33 patients) 2 pads
   3% (1 of 33 patients) pad reduction
  ≥50%

- 12.1% (4 of 33 patients) treatment failure
- After 16.6 months following repeat sling:
- 34.5% (10 of 29 patients) no pad

- 37.9% (11 of 29 patients) 1 dry
  "security" pad
   3.4% (1 of 29 patients) 1 wet pad
   3.4% (1 of 29 patients) 2 pads
- 10.3% (3 of 29 patients) pad reduction ≥50%
- 10.4% (3 of 29 patients) -failure.

Conclusion: Repeat sling is an effective option after failed first sling.

Soljanik et al. Eur Urol. 2010 Nov;58(5):767-72.

# SALVAGE T-O SLING FOR RECURRENT PPI

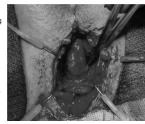
- 18 patients: Failed early (10), Failed late (8) (>12 months)
- At 6 m success (72%), Dry (50%)
- At 17 m success ( 56%), Dry (39%)
- At 6 m, Late primary failure had better outcome than early (75% vs. 30%; p= .031)

Conclusion: Salvage AdVance male sling is a viable option after a failed primary male sling especially after a prolonged efficacy period.

Martinez et al. UROLOGY. 2015: 85(2): 478-82

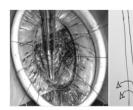
# RE-SLING (T-O) PEARLS

- Dissect corpus spongiosum distal to sling Virgin plane
- · Identify distal aspect of sling
- Right angle clamp around sling arms Transect sling arms and excise sling off urethra
  - Repair corpus spongiosum with absorbable suture
- Pass new trocars and place sling slightly
- distal to first sling
   Chung ASJ et al, Transl Adrol Urol, 2017



# REVISION (QUADRATIC) PEARLS

- Imbrication of prior sling
- Place #1 Prolene plication sutures superficially into fibrous mesh Similar to penile plication imbrication sutures
- Three sutures
  - · Initial suture at base of inverted mesh triangle
  - Leading edge of sling
     Rubin RS, et al: Transl Androl Urol, 2017
- Tensioning via RLPP
- RLPP measurement and sling fixation improves sling outcome
  - 70% vs 39% much/very much better at 25 months
    - Sourial MW. et al: CUAJ. 2017
    - Comiter, et al, Urology, 2015

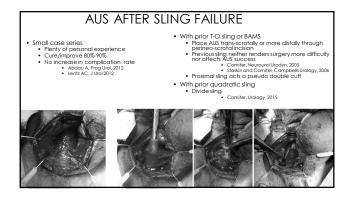


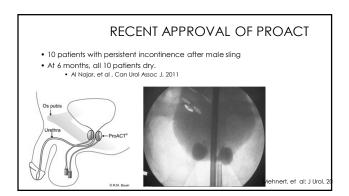
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# RADIATION AND MALE SLING

- Bulbourethral Northwestern Sling
   Prior irradiation was the only identified factor that predisposed to sling failure
- to sling failure

  Without radiation 68% success (37/59)

  With radiation 29% success (2/7)

  Schaeffer AJ, J Urol, 1998
- Schaeffer AJ, J Urol, 1998
   Bone anchored male sling (BANS)
   Previous full-course EBRT decreases efficacy of bulbourethral sling
  - sling

    Castle, 2005; Onur, 2004; Comiter, 2004

    Generally 75% BAMS success without XRT

    Generally <50% BAMS success with XRT
- Quadratic sling

  - Quadratic String

    Scant data

    Trial did not exclude men with XRT

    No difference in outcome with and without XRT

    Comiter, Urology, 2014

# RECENT PUBLICATION: RETROURETHRAL SLING +/- XRT

Overall 37 patients, avg f/u 17.3 months 19 (51.4%) dry, 10 (27%) improved, 4 (10.8%) failed

140	XIX I	AICI	
• Cure	63.3%	• Cure0%	
• Improved	26.7%	<ul> <li>Improved</li> </ul>	28.6%
No change	e 6.7%	No change	e 28,6%
<ul> <li>Worse</li> </ul>	3.3%	<ul> <li>Worse</li> </ul>	42.9%
<ul> <li>Success</li> </ul>	90%	<ul> <li>Success</li> </ul>	28.6%
<ul> <li>Failure</li> </ul>	10%	<ul> <li>Failure</li> </ul>	71.5%

Torrey et al: Urology 82:713, 2013

# AUS AND XRT

- Erosion
  - Generally agreed higher erosion rate
  - · Risk of erosion has not diminished despite improvement in XRT technique Hird AF, Radomski SB, Can Urol Assoc J, 2015
- · Mixed data on continence
  - But with revisions, ultimate success rate is similar

    - Hoy NY, Rourke KF, Urology, 2015
       Mottet N, et al, Urol Int, 1998
- Recommended to use lower pressure reservoir and/or prolonged deactivation
   Martins FE, Boyd SD, J Urol, 1995

Trans-Obturator Sling Advantage over Quadratic Sling

- Easier Technique
- Faster surgery
- Lowers infection risk
- Potentially less pelvic pain No pain from pubic rami under tension
- Detrusor hypocontractility not a contra-indication

Quadratic Sling Advantages over T-O sling

- Dual mechanism of action
  - T-O urethral elevation/relocation
     P-P urethral compression
- Quadratic fixation more reliable than 2-point fixation
- Broader compression
- Potentially more efficacious for more severe leakage
- Inside-out passage minimizes risk of urethral injury
- Efficacious for more severe leakage

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#### Trans-Obturator Sling Disadvantages

#### Quadratic Sling Disadvantages

- Not proven for severe incontinence
- Outside-in passage theoretically risks urethral injury
- Urinary retention rate 3-21%
- High failure rate if fixation fails
- More pain than retroluminal
- Need normal detrusor contractility
- Needs to be incised/excised prior to AUS

#### CLINICAL SCENARIOS WHERE AUS IS PREFERRED

- High volume SUI
   > 450 g/day
   Fischer et al 2007
- - Sling with poor success post AUS
     Tuygan et al, 2009; Comiter et al, 2002; Castle et al, 2005
- Dr. or Patient Preference/Predictable success with AUS
  - Best chance of "cure"
     90% satisfaction with AUS regardless of degree of incontinence
- · History of radiation

  - Sling offers lower rate of success
     Castle et al, 2005; Onur et al, 2004; Comiter et al, 2004

#### SLING IS PREFERRED FOR MOST PATIENTS WITH MILD TO MODERATE LEAKAGE

- Intermediate term data with male sling
  - Sling equally efficacious with lower rate of severe complication in patients with mild-moderate SUI
    - If they have not failed previous AUS, no xrt, normal bladder contractility  $6^{th}$  ICI, 2018
    - Patients generally choose sling over AUS • When given a choice, 92% choose sling
      - When recommended AUS, 25% still che
         Kumar A, et al: J Urol, 2008

#### WHAT SHOULD YOU OFFER?

- $\bullet$  Best to offer what is best, or either if either is  $\ensuremath{\mathsf{OK}}$ 
  - ISD, weak bladder --- AUS (consider T-O sling if mild)
  - Severe incontinence --- AUS

  - Unlikely to have predictable success with T-O sling
     Quadratic sling should be considered for severe leakage if patient refuses AUS
  - Moderate leakage, normal bladder -- Quadratic sling
  - AUS still OK after sling failure
     Sling contra-indicated after AUS failure
  - Mild incontinence --- T-O sling

  - XRT AUS
- Revision surgery AUS

## **Urinary Fistula in Female Pelvic Reconstruction**

Comprehensive Review of Urology August 7th, 2018

Elise J.B. De, MD Massachusetts General Hospital



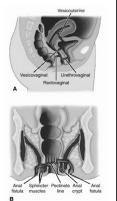
#### Objectives

- · Diagnosis and management of Fistula
- · Factors impacting fistula
- · Surgical principals surrounding repair

#### **Fistula**

Definition: Abnormal communication between two epithelialized surfaces

- · Vesicovaginal fistula
- Recto-vaginal fistula
- Urethrovaginal fistula
- Ureterovaginal fistula
- · Vesicouterine fistula



#### Fistula Biology

- · All types share a common etiology
- Ischemia / Necrosis
  - Macrovascular
  - Microvaso
     Infectious
- Impaired Healing
- Poor Nutrition
- Inflammation
- Pressure differential between compartments in context of decreased resistance
- · Epithelialization of mature tract

#### Vesicovaginal Fistula - History

- Egyptian times
  - First mentioned in the Ebers Papayrus
  - Advised against attempts to treat
  - Noted in mummy of Queen Henherit 2050 B.C.
- Avicena in 950 A.D.
  - Noted correlation between prolonged labor and fistula
- · Renaissance Period
  - Term 'Fistula' coined by Luiz de Mercado in 1597
  - Surgical treatment: topical silver nitrate (~ universal failure)
  - Falto:1st successful repair late 1600s
    - denudation of tract and re-approximation using sharpened swan quills

#### Vesicovaginal Fistula - History

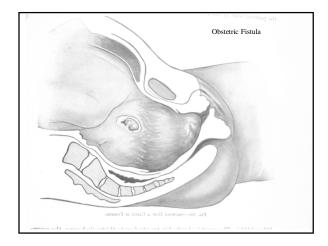
- 1852 Sims
  - successful closure using leaden and silver suture with drainage catheters on his 30th attempt, a slave by the name of Anarcha
- 1861 Collis
  - introduced the concept of a layered closure
- 1890 Trendelenburg
- pioneered the Transabdominal approach
- 1914 Leguen
  - developed the Transvaginal approach
- 1920 Martius and Garlock
  - developed the concept of interpositional tissues
- 1954 Falk and Trancer
  - recommended routine use of urinary catheter drainage

#### Etiology of Vesicovaginal Fistula

- Developing Countries
- Birth Trauma
  - Prolonged Labor
  - Tissue necrosis of bladder base and urethra with substantial tissue loss
- Bilharziasis

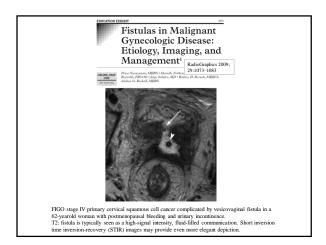
- Industrialized Nations
- 75% due to injury at the time of gynecologic, urologic, or other pelvic surgery (Tancer, 1992).
- Most commonly -Inadvertent suture incorporation of vaginal cuff tissue into an unappreciated bladder wall injury
- Tissue necrosis promotes fibrosis and induration

Tancer ML: Observations on prevention and management of vesicovaginal fistula after total hysterectomy. Surg Gynecol Obstet 1992; 175(6):501-5 Wall LL: Obstetric fistulas in Africa and the developing world: new efforts to solve an age-old problem. Womens Health Issues 1996; 6(4):229-234.



#### Other Causes

- Radiation
- Malignancy
- · GI Surgery such as Low Anterior Resection
- · Inflammatory Bowel Disease
- Urinary Tuberculosis
- Foreign Body
  - Pessaries
- Birth Control Devices IUD, Diaphragms
- Autoimmune diseases such as Behcet's (vasculitis-related bladder wall necrosis)
- CO2 Laser Ablation of Cervical Lesions
- Pelvic Fracture (2%)



#### GU Injuries and Hysterectomy

• Ureteral Injury: 6.2/1,000 cases

• Bladder Injury: 10.4/1,000 cases

• Incidence of VV fistula after Hyst: 0.1%

- -1/1300
  - Highest in Laparoscopic (1/455)
  - Lowest in Vaginal (1/5636)

#### Ureterovaginal Fistula

- 10% risk of simultaneous ureteral component
- Ureter most likely to be injured at
  - Level of infundibulopelvic ligament
  - Ligation of uterine vessels



#### Risk Factors for VV Fistula

- Diabetes
- Smoking
- Prior Caesarian Section/Previous Pelvic Surgery
- PID or Concurrent Infection
- Endometriosis
- PVD
- · Concurrent Infection
- · Malignancy
- Trauma
- · Pelvic Radiation
  - Can be seen up to 20 years after irradiation

#### Presentation of Fistula

- Usually within 7-21 d
- Incontinence
  - Pseudo-Stress
  - Vaginal Voiding (urethrovaginal fistula)
  - Continuous Incontinence not always
- Ilens
- Pain (ureterovaginal)
- Hematuria
- Vesicouterine: incontinence, amenorrhea, cyclical hematuria

#### Differential Diagnosis of Post-Hysterectomy Vaginal Drainage

- Fistula
- Posthysterectomy Pseudoincontinence
- (leakage of peritoneal fluid from a vaginal cuff sinus tract)
- Fallopian Tube Drainage
- · Lymphatic Fistula
- True Incontinence
  - Detrusor Instability
  - Poor Bladder ComplianceStress Incontinence
- Vaginal Secretions
- · Vaginal Infections
- Vaginal Voiding

#### Work-up

- Physical Examination
  - Fluid pooled at cuff
  - Identify presence and location of fistula
  - Assess vaginal capacity
  - Evaluate for induration or fibrosis
  - Rule-out pelvic organ prolapse
- Dye Testing (may combine)
  - Tampon Test
    - Oral Pyridium shows as orange on tampon
  - Bladder Instillation
    - With methylene blue or sterile milk
    - Better test for localization
  - Combination can help with ureterovaginal

#### Work-up

- Cystoscopy
  - Demonstrates size, location, multiple
  - Assesses for edema and necrosis
  - Allows for biopsy if question of malignancy
  - Can be combined with dye testing e.g. Indigo Carmine
- Routine preoperative ureteral imaging
  - RTGP
  - IV Urography
  - RUS misses up to 20% of ureteral injury
- · Assess induration, fixation to bone
- Dual balloon catheter (Trattner catheter)
- EUA

#### Radiographic Evaluation

- VCUG
  - Evaluates for complicating factors such as reflux, cystocele, urethral involvement or urethral diverticulum
- Retrograde Pyelogram
  - Highest diagnostic accuracy for evaluation of ureteral involvement
- MRI

#### Urethrovaginal Fistula



#### Urethral Fistula

- Etiologies:
  - Anti-incontinence procedures (mesh)
  - Gynecologic surgery
  - Low Anterior Repair
  - Urethral Diverticulectomy (most common)
  - Urethral catheter trauma
  - Prolonged obstructive labor
  - Pelvic fracture trauma
- Often not apparent until after foley catheter removed

#### Urodynamics in Fistula Patients

- Advised by many (including this author)
  - Fistula formation (and recurrence) may be related to bladder factors
  - If further surgical therapy is indicated, can be planned simultaneously
- Over half of women have concomitant findings
  - In a study by Hilton et al. in 1998
    - 47% had stress incontinence
    - 44% had detrusor instability
      17% had poor bladder compliance

- Pre-Op Endoscopic Evaluation
- Cystoscopy
- · Retrograde Pyelograms
- Speculum Exam with:
  - Lonstar Retractor
  - Methylene Blue
- · Plan Formal Repair Thereafter

#### Obstetric Fistula

- Prior to 1900, the most common cause of VVF in the U.S. was obstructed labor (Stothers et al, 1996)
- In the developing world, VVF most commonly occur as a result of prolonged obstructed labor due to cephalopelvic disproportion, with resulting pressure necrosis (Arrowsmith et al, 1996)
- "Obstructed labor injury complex": urethral loss, stress incontinence, hydroureteronephrosis, renal failure, rectovaginal fistula, rectal atresia, anal sphincter incompetence, cervical destruction, amenorrhea, pelvic inflammatory disease, secondary infertility, vaginal stenosis, osteitis pubis, and foot drop (Arrowsmith et al, 1996).

Arrowsmith SD: Genitourinary reconstruction in obstetric fistulae. J Urol 1994; 152(2 Pt. 1):403-406 Stothers L, Chopra A, Raz S: Vesicovaginal fistula. In: Raz S, ed. Female urology, 2nd ed. Philadelphia: WB Saunders; 1996:490-506.

#### Obstetric Fistula

- Some estimates place the worldwide prevalence as high as 2 million women worldwide.
- In some rural areas of Africa, the fistula rate may approach 5-10 per 1000 deliveries, which is close to the maternal mortality rate in Africa.
- An estimate of up to 500,000 new cases of obstetric fistula occur throughout the world annually (Hilton, 2003), although the total morbidity from obstructed maternal labor has been estimated to be in excess of 5 million individuals annually (Kelly, 1991)
- 96.5% of 932 VVF seen at a single hospital in Nigeria over a 7-year period were temporally associated with labor and delivery (Wall et al, 2004).

Wall L, Arrowsmith S, Briggs ND, Browing A, Lassey A. The obsteric vesicovaginal Fistula in the developing world. In: PA, LC, S, K, AW, editors. Incontinence. Paris: Health Publications; 2005, p. 1403-54. Wall LL: Obsterfic Estudas in Africa and the developing world: new efforts to solve an age-old problem. Womens Health Issues 1996; 6(4):229-234.

#### Fistula Worldwide

- Cephalopelvic disproportion:
  - Fetus is impacted 3 to 5 days
  - Fetus dies 85% of the time leading to softening and delivery
  - The woman, if she survives, can be left with a fistula
- Other etiologies:
  - Trauma
  - Sexual abuse
  - Coital injury in child brides
  - Female genital mutilation



Hilton P: Vesico-vaginal fistulae in developing countries. Int J Gynaecol Obstet 2003; 82(3):285-295 Kelly J: Fistulae of obstetric origin. Midwifery 1991; 7(2):71-73

United Nations Population Fund (UNFPA) and the United Nations International Children's Educational Fund (UNICEF) Survey:

- Each African country surveyed had only one emergency obstetric center per 500,000 inhabitants
- Only 8-35% of women with complications during labor received care at an appropriate facility
- Even when the patient arrives at the facility, good care is not a guarantee. Most emergency care requires payment.

Lewis G, deBernis L, editors. Obstetric fistula: guiding principles for clinical management and programme development. Geneva, Switzerland.: WHO; 2006, p. 78.

#### Maine's Three Delays

- 1-Delays in the decision to seek care influenced by socioeconomic and cultural factors (need to obtain permission from a husband or male family member to seek care)
- 2- Delayed arrival at the health facility (Road conditions, transportation and communication deficiencies)
- 3- Delayed provisions of adequate care at the facility may be due to lack of staff, supplies, or electricity or inability to reach a surgeon





#### Fistula



- Estrangement from spouse / social life. Patients often live with willing relatives
- In addition to discomfort from the continuous soiling, these women are
  often rejected by their husband, their family and their community. They
  cannot use transportation, walk for long periods of time, stand outside with
  friends, cook, participate in social and religious events, or go to the mosque
  or church.
- Since most of these women are left without children, they feel that they
  cannot fulfill their role as a woman, a wife or a mother. Most have trouble
  finding work. The combination of social and economic forces in many of
  these cases compounds the woman's preexisting poverty, and
  malnourishment is the rule. These physical and psychological factors
  impact the success of surgery in the percentage of women who find
  treatment.

## Incidence & Risk factors Obstetric fistula

- Between 0.1% to 1.5/1,000 deliveries in rural areas.

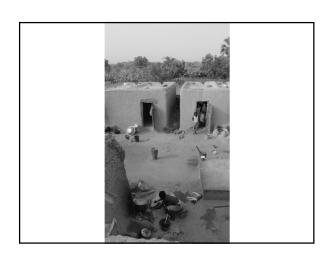
  Major risk factors appear to be:
- Age at first marriage
- Short stature
- Pregnancy with a male child
- Failure to attend antenatal care
- Low socio-economic status
- Low social class
- Lack of employment and illiteracy.



#### Setting for Delivery

- Wife lives with husband's family
- Mother in law or 1st wife attends delivery
- Distance to C section is 1 day walk

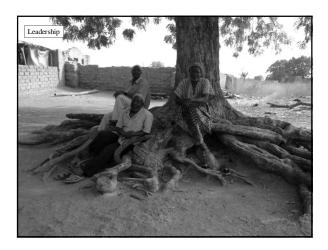












#### Hospitals



Centre Medical avec Antenne Chirurgicale (C.M.A.) de Boromo

#### Many Developing Facilities Lacking

- Diagnostics
  - UrodynamicsCTMRI
- Medications
  - Anticholinergics
  - Antibiotics
- Botox • Supplies
  - CIC
- Irrigation (e.g. AugmentSophisticated techniques
- Augment, Catheterizeable stoma, AUS
- Physiotherapists/ Nurses
   Voiding dysfunction not addressed















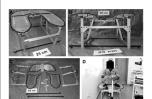


Int Urogynecol J (2015) 26:749-755 DOI 10.1007/s00192-014-2575-7

ORIGINAL ARTICLE

Validation of a culturally compliant voiding platform for urodynamics in African vesicovaginal fistula patients

Ali Borazjani • Helina Tadesse • Fekade Ayenachew • Howard B. Goldman • Margot S. Damaser • L. Lewis Wall



Only the heel-to-heel distance (H-H) measure of posture was significantly increased on the platform compared with on the ground.

#### Management

#### Conservative Management

- Urethral Catheter Drainage and Anticholinergics
- · Success less likely with
  - mature tracts (>7 d)
  - Large defects > 5-10 mm
  - Malignancy or radiation
- Success rate 2-20 %
  - Trancer 1992
  - Dmchowski 2006
  - Telinde's Operative Gynecology 7<sup>TH</sup> ed. 1992

#### Cystoscopic Treatment

- Fulguration
  - 73% success rate with fistulas < 3mm in size
    - 2 weeks of catheter drainage post-op
    - -Stovsky 1994
- Cystoscopically placed suture closure described by McKay in 1997
  - Has not gained popularity

#### Fibrin Glue

- Use of fibrin glue as an interpositioning layer during the vaginal anatomical repair of complicated vaginal fistulas
- Alternative to the use of Martius flaps interpositioning.
- Decreases operative time and adding simplicity to the already complicated procedure are additional values of using this procedure.

Safan A, Shaker H, Abdelaal A, Mourad MS, Albaz M. Fibrin glue versus martius flap interpositioning in the repair of complicated obstetric vesicovaginal fistula. A prospective multi-institution randomized trial. Neurour

#### Fistula Repair Standard Principles

- · First operation is best chance
- Ureters should be evaluated identified and protected
- Fistula should be widely mobilized, closed without tension
- Repair must be water-tight and infection free
- · Martius flap or other graft should be considered in complex cases.
- Evaluate sphincteric mechanism (anti-incontinence ?later).
- $\bullet \quad \text{Associated Vagino-rectal fistulae (repaired simultaneously} \pm \text{colostomy}).$
- After repair, drain 10-14 days

#### Simple Fistula

- 20% of obstetric fistulas are simple.
- Less than 3 cm in diameter
- No or only mild scarring
- Do not involve the urethra.

Johnson K. Int J Gyuncoci Obstet. 2007 Nov;95Suppl.15.12:9.

Nadia PM, J ObstetGyuncoci B Ern. pp. 152, App;93.11.6.

Azir S. A.J ObstetGyuncoci B Ern. pp. 152, App;93.11.6.

Azir S. A.J ObstetGyuncoci B Er. Commenw. 1965 Oct.725;76:58.

Ashnooth FL. West Af Med J Nigw Med Deet Pract. 1973 Apr;22(2):29-43.

Waadiji K. The (surpical) management of bladder fitatula in 75 women in northern Nigeria [Doctoral]. Utrecht, Netherlands: Utrecht; 1989.

Arrowninis D.J. 1011. 1984 Aug;152(2): p. 11;30:66.

Krichum R.G. J ObstetGymacol B Ernp. 1949 Pech-56(1):2-7.

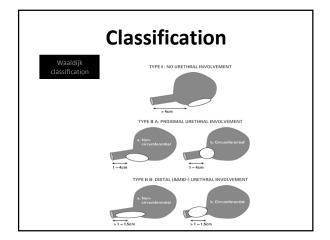
Abbett DI Esta Ark Med. J 1959 Mar;57(2):100-18.

Lavery DW. J ObstetGynacol B Ernp. 1955 Aug;52(4):55:100-98.

Maddian K.J ObstetGynacol B Ernp. 1955 Aug;52(4):55:100-99.

#### Complex Fistula

- > 4-5 cm in diameter
- Involvement of urethra, ureter, rectum
- Juxtacervical with incomplete visualization of the superior edge
- Previous Failed Repair



#### Surgical Therapy

- "First attempt is most likely to succeed"
- 1st attempts meet with 90% success
- · Factors that affect success
  - Etiology
  - Duration
  - Presence of necrosis or infection
  - Surgeon experience
    - -Dmochowski 2006

#### Timing of Repair

- · Classic Dogma
  - Wait 3 to 6 months before surgical attempt at closure
  - Those encountered in first two days should be immediately repaired
- Some now trying earlier repairs
  - Transvaginal approach to apical fistula success in 94% in patients up to 6 weeks out from injury
    - Select patients
    - Not done immediately post-op

Hadley et al 1990

#### **Preoperative Preparation**

- Treat any Infections
- Antibiotics
- Estrogen replacement if indicated for 4 to 6 weeks pre-op

#### Surgical Approaches

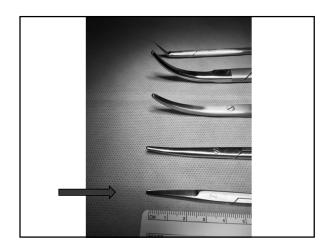
- Transvaginal
  - Associated with decreased operative time
  - Less morbidity
  - More rapid recovery
  - Difficult with fibrosis or pelvic immobility
  - Difficult with larger defects
  - Greater risk of ureteral injury
- Abdominal
  - Better with a poorly visualized tract
  - Difficult with a narrow or immobile vagina
  - Easier for large defects
  - Allows other procedures at same time (e.g. reimplant)
  - Less risk of ureteral injury

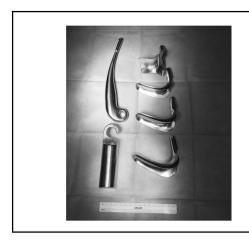
#### Vaginal Approach

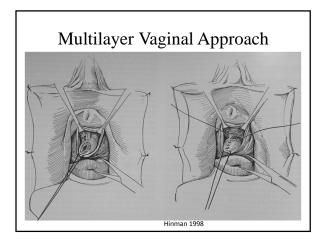
- Catheters
  - Suprapubic
  - Urethral
  - Ureteral
- Intraoperative Cystoscopy
- Self retaining retractor
- Small balloon catheter through fistula tract
- U or J type Vaginal incision incorporating base of fistula tract into the flap
- · Vaginal mucosal flap oriented anteriorly
- · Lateral relaxing incisions often required

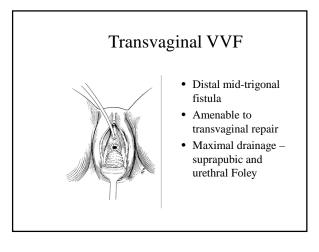
#### Vaginal Approach

- · Fistula tract circumscribed but not widely excised to avoid a wide defect
- · Wall opposite flap dissected to allow advancement of flap beyond defect
- · Fistula tract closed with full thickness bites of bladder (1st layer)
- · Second layer is prevesical fascia closed at a 90 degree angle
- · Flap is an option
- Integrity is tested by filling the bladder
- Third layer closed by advancement of vaginal tissue over suture lines



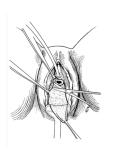


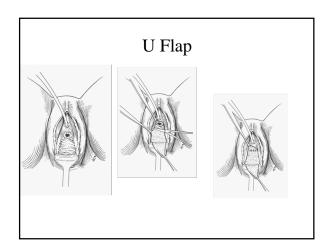




#### Transvaginal VVF - 2

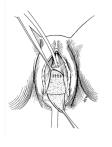
- Development of Uflap with the fistula forming the apex
- Advancement of the vaginal flap at the completion of the procedure

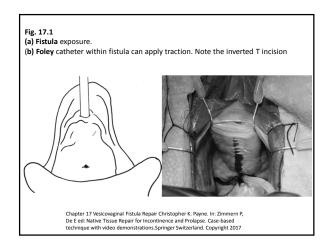


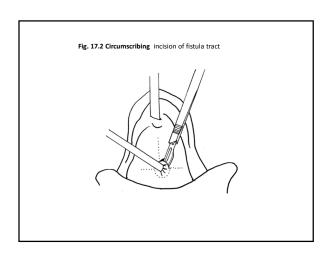


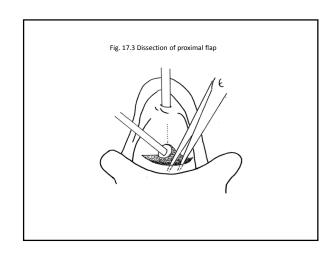
#### Transvaginal VVF

- 1st layer- Transverse closure of the fistula including the tract (without excision); interrupted 3-0 or 4-0 vicryl
- 2<sup>nd</sup> layer imbrication of perivesical fascia









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Fig. 17.4 Proximal flap is dissected to the apex and lateral flaps to the pelvic sidewall. Observe the 2 cm radius around the fistula



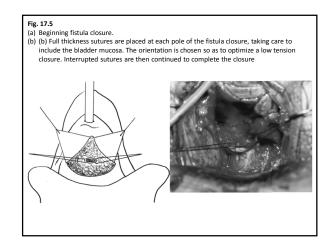
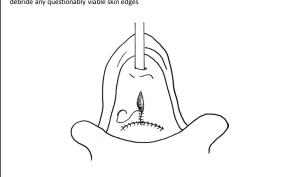


Fig. 17.6 Skin closure. In many cases the posterior flap can be advanced much farther anteriorly when there would otherwise be inadequate skin to close without tension. Always debride any questionably viable skin edges



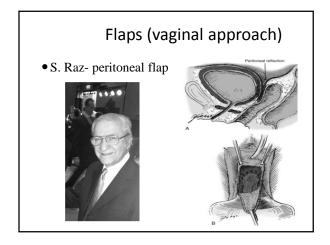
#### Is vascularized tissue necessary?

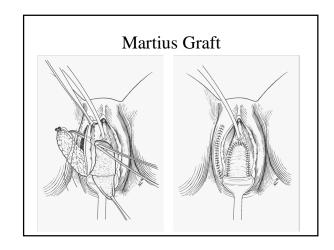
- Fistula size > 2 cm
- Recurrent fistula
- Radiation

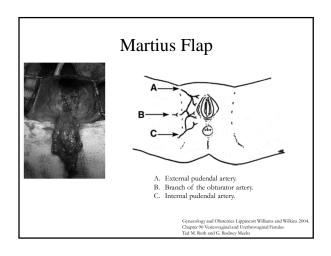
Eilber KS, et al. J Urol 169, 1033–1036, March 2003

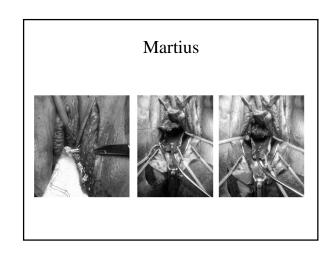
	Abdominal Approach	Vaginal Approach
Use of adjunctive flaps	Omentum, peritoneal flap, rectus abdominus flap	Labial fat pad (Martius fat pad), peritoneal flap, gluteal skin or gracilis myocutaneous flap
Relative indications	Large fistulae, location high in a deep narrow vagina, radiation fistulae, failed transvaginal approach, small-capacity bladder requiring augmentation, need for ureteral reimplantation, inability to place patient in the lithotomy position	Uncomplicated fistulae, low fistulae

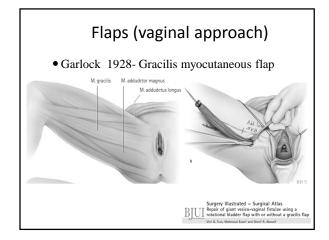
# Flap Interposition – Vaginal Approach • Martius flap • Peritoneal flap









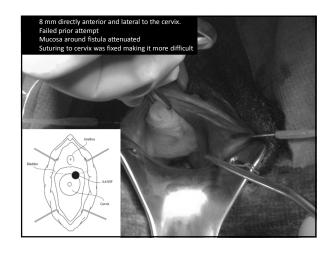


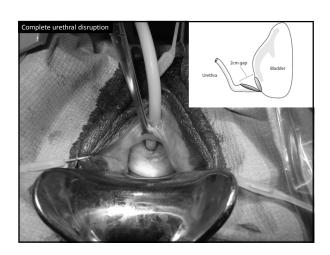
#### Alternative Vaginal Procedure

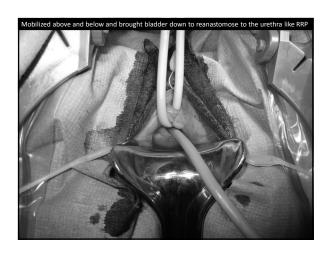
- For poor operative candidates or those with deep and elastic vagina
  - Excision of epithelium around the fistula site
  - Colpocleisis several layers of suture across the vaginal walls, obliterating the vagina around the fistula
  - Vaginal depth is compromised by this
  - +/- Dyspareunia

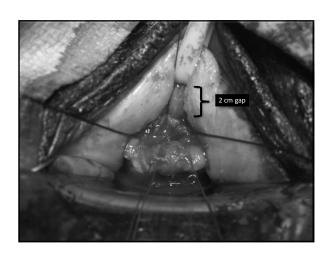
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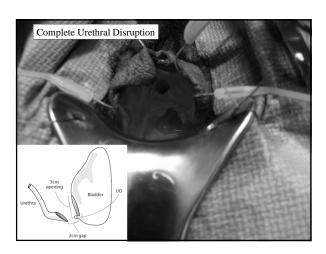










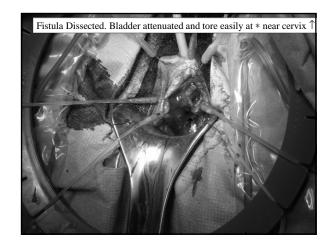


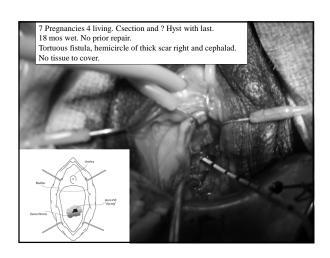
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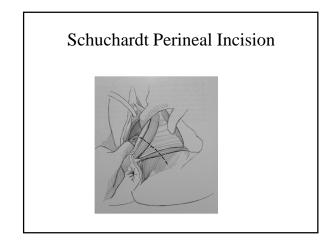


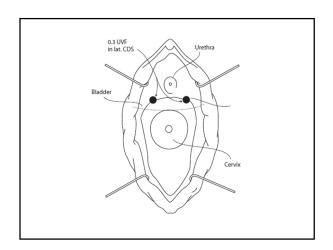


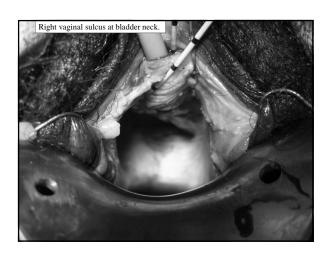


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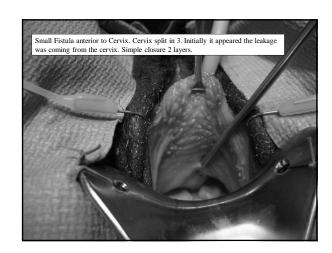












#### Postop Care

- · Bladder relaxation with anticholinergics
- Catheter drainage 3 weeks
- · VCUG to confirm closure then foley removed
- If drainage resumes when foley is removed replace
- No intercourse for 2 months
- · Continue estrogens

#### Success Rates Obstetric Fistula

 The advantage of having the fistula well repaired the first time is crucial because success rate decreases with more attempts of repair:

First repair success rate: 70-90%2nd repair success rate: 50-60%

>than 2 procedures: <40%

Mourad, Chapter 18

#### Risk factors for persistent incontinence:

- 1) Urethral Involvement (OR 8.4)
- 2) Large Fistula (OR 1.3 for each cm)
- 3) Severe vaginal scarring (OR 2.4)
- 4) Small bladder size (OR 4.1)
  - Of note, patients cannot afford anticholinergics

Browning A. Risk factors for developing residual urinary incontinence after obstetric fistula repair. BJOG 2006; 113:482-485.

In patients in whom all of the risk factors mentioned above are present, the postoperative incontinence rate may approach 100% [ ,35].

#### Success

- Fistulas can be closed successfully in 72% to 92% of cases.
  The definition of success, however, is often different when
  the perspectives of the patient and the surgeon are
  compared. "Success" to a fistula patient means complete
  restoration of urinary continence and control, whereas many
  surgeons define "success" as simply closing the fistula
- Estimates of persistent urinary incontinence after a successful closure of the fistula:
  - 16.3% in a large retrospective review of patients by Wall et al
  - 33% in a small series of complex fistulas in which the proximal urethra was lost

Wall L, Arrowsmith S, Briggs ND, Browing A, Lassey A, Fistula in the developing world. In: PA, L C, S K, A W, editors. Incontinence Paris: Health Publications; 2005, p. 1403-54. Gendry RR, Creaga AA, Romenberg ML, Wheeless CR. . Int J Gynaecol Obstet. 2007 Nov;99Suppl1:S51-6.

#### Complications

- Cicatrix leading to:
  - Vaginal stenosis and
  - Dyspareunia
- · Persistent Fistula
  - Secondary repair to be done only after post-op inflammation has resolved

#### Urethral Fistula Repair

- Distal
  - Extended meatotomy
- · Small to Intermediate
  - Tension-free layered closure
- · Debilitated patients
  - Bladder neck closure with catheterizable stoma
  - Circumferential closure at bladder neck by complete disruption of the endopelvic fascia & layered inverting closure of the urethral stump

#### Surgical Repair Urethrovaginal Fistula

- · Suprapubic tube recommended
- · Inverted U or J incision
- · Flap raised to level of bladder neck
- Lateral dissection should be accomplished to perforate the endopelvic fascia for purposes of placement of sling or suspension sutures
- · Fistula tract circumscribed but not excised
- Margins apposed with running 3-0 or 4-0
- Second layer incorporates periurethral tissues
- Vaginal flap closure
- +/- Interposition tissue

#### Vaginal Flap Urethral Reconstruction

- 14 Fr urethral catheter placed
- Inverted U with apex just proximal to the meatus
- Neourethra created using 2 parallel incisions on either side of the meatus
- Flaps are mobilized laterally and tubularized around the catheter
- Closed with a running locking 4-0 suture
- Interposition tissue utilized



#### **Concomitant Sling**

- Beneficial effects on urethral function (closure)
- Also adds interpositional tissue
- Some advise empiric placement given high rate of stress incontinence

#### Outcomes

- 50% dry without a simultaneous antiincontinence procedure
  - Khanna 1992
- 87% continent with sling
  - -- Blaivas et al. 1996
- Urethral stricture may result

#### Abdominal Technique

- Does not work for fistulas extending to the urethra
- Good for bladder concurrent augmentation or reimplantation
- May be approached extra-peritoneal or intraperitoneal with bisection of the bladder to the level of the fistula.
- Ureteral catheterization.
- Bladder and vagina are mobilized and separated by dissection along the vesicovaginal septum (difficult)
- · Tract is completely excised
- Posterior bladder flap mobilized to repair vaginal defect
- · Interposition of omentum if intraperitoneal

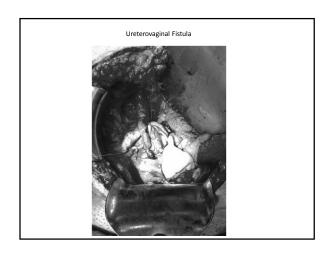
## Transabdominal Repair (O'Connor)

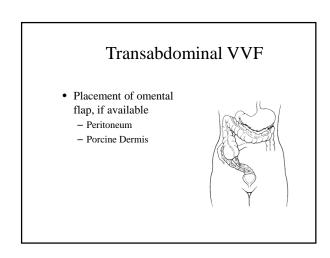


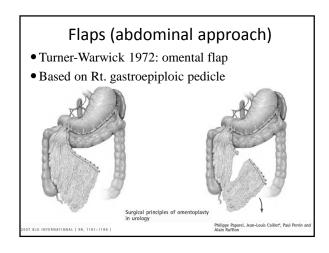
- Traditional approach large cystotomy to the level of the fistula
- Development of space between the cystotomy and vaginal side of fistulous tract

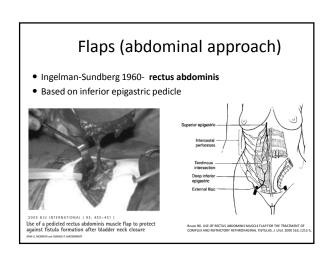


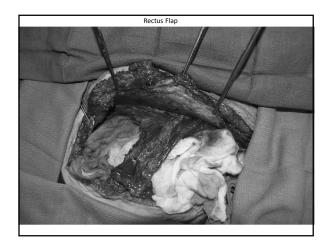


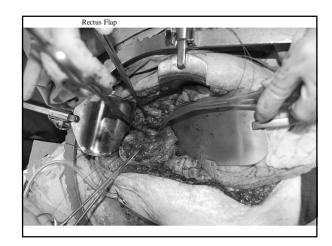












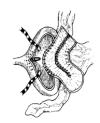
#### Tissue Loss

- In some cases pressure necrosis may destroy virtually the entire bladder, so that if the defect can be closed at all, the afflicted woman is left with a remarkably small (30 50 ml) bladder that compliance may be altered by the extensive fibrotic changes that often take place.
- To date there have been few urodynamic studies reported on patients who have undergone successful fistula closure

Schleicher DJ, OjengbedeOHA. International Urogynecology Journal 1993;4:262-5. Carey MP, Goh JT, Fynes MM, Murray CJ. Am J Obstet Gynecol. 2002 May;186(5):948-53.

#### Compliance/Capacity

- Integration of augmentation into the repair of the fistula
- Diversion
  - +/- cath stoma
  - +/- cystectomy



Tabakov ID, Slavchev BN. J Urol 171, 272–274, January 2004

#### Cervical Cancer

- Retrospective review 2096 pts treated for cervical cancer /10 y
  - 38 patients (1.8%) developed fistula (Emmet et al)
  - All had undergone previous radiation therapy.
- Reported annual incidence of XRT- VVF 1%-5% (Angioli)
- May occur up to 30 years after XRT treatment (Zoubek et al)

Emmert C, Kohler U. Arch Gynecol Obstet 1996;259:19–24. Angioli R, Penalver M, Muzii L, et al. Crit Rev Oncol Hematol 2003;48:295–304. Zoubek J, McGuire EJ, DeLancey JO. J Urol 1989;141:1347–1349.

#### **Exenterative Surgery**

- Retrospective review spanning 45 years (Berek et al, UCLA):
  - Among 75 patients who underwent exenterative surgery (most of whom simultaneously underwent reconstruction of the bladder, vagina, or colon)
  - 17 (23%) developed intestinal or urinary tract fistulas.
- Postoperative fistulas typically occur 10–20 days after surgery (Avritscher) but also may manifest in the immediate postsurgical period.

Berek JS, Howe C, Lagasse LD, Hacker NF. Gynecol Oncol 2005;99:153–159. Avritscher R, Madoff DC, Ramirez PT, et al. RadioGraphics 2004;24(suppl 1):S217–S236.

#### Neobladder Fistula





#### Neobladder Fistula

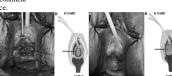


UROLOGY 81 (1), 2013 Reconstructive Urology

Vaginal Repair of Pouch-vaginal Fistula After Orthotopic Bladder Substitution in Women

- 298 women underwent orthotopic neobladder after radical cystectomy.
- 8 PVF (2.7%) were diagnosed

  - 5 of 100 (5%) before and
    3 of 198 (1.5%) after technical modifications (to be discussed).
- · Transabdominal repair 2 and vaginal repair in 6
- At mean 146 months:
  - All repaired patients were continent
    1 had nocturnal incontinence.



**Modifications** 

Vaginal repair of neobladder-vaginal fistula: a case report and review of the literature

Katherine Gelber - Justin Bohrer - Charles O. Kim -Steven Minaelia

- Bestard Vallejo [23]: 8-mm fistula at the urethro–ileal anastomosis:
  - Vaginal approach using a two-layer closure
  - Martius flap interposition
  - No reappearance after 1 year.
- Pruthi et al. [15]: two patients who developed NVF after collagen
  - NVFs at the level of the bladder neck were repaired transvaginally
  - 3 layers and Martius flap interposition
- Cadaveric fascia pubovaginal sling with infrapubic bone anchors

Successful experiences using omental, peritoneal, or (Martius) flaps [19–21].

Vaginal repair of neobladder-vaginal fistula: a case report and review of the literature

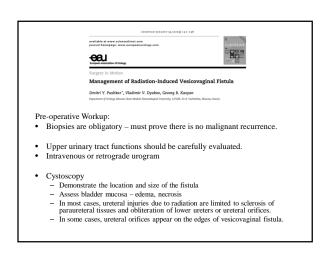
- Risk of injury greatest:
  - Most distal dissection of the vesico-vaginal plane near urethra
  - Poor vascularity or radiation therapy
- · Prior recommendations:
  - Dissect urethral and vaginal stumps separately to have easy anastomosis
  - Minimize blunt dissection in the vicinity of the bladder neck and sharply dissect the posterior urethra
  - Preserving the anterior vaginal wall during cystectomy
  - Avoid overlapping suture line between vagina and bladder neck
  - Omental flap interposition may help to avoid future fistulization

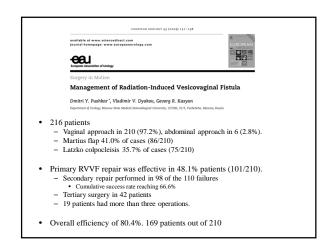
Kumar A, et al, 2009: Saudi J Kidney Dis Transpl 20:658-661 Rapp DE et al, 2004: BJU Int 94:1092-2095

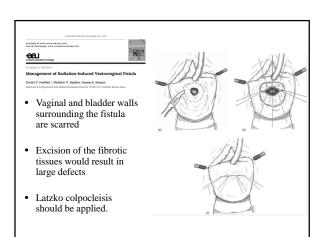
æu

Dmitri Y. Pushkar\*, Vladimir V. Dyakov, Gevorg R. Kasyan

- · Pelvic radiation: primary cause of delayed vesicovaginal fistula
- · Fibrosis occurs in the bladder lamina propria.
- Hyalinization of the connective tissues (radiation fibroblasts)
- Small and medium arteries: obliterative arteritis.
- · Atrophy or necrosis of the bladder epithelium
- Ulceration or fissures form.
- Majority present 1.5-2 yr after radiotherapy







#### Radiated Fistulas

- Periodically assess pre-op given propensity of these to evolve over time
- Wide excision and tissue interposition
- Fistulas may occur up to 20 y following XRT
- Gracilis Flap best interposition tissue
- 50% -80 % success
  - Raz 1992
  - Bissada 1998

#### Timing of Repair after Radiation Fistula

- Allow for resolution of necrosis and inflammation up to 1 year
- Strongly consider interposition of vascularized tissue
- Success rates 40-100% (Level 3 Evidence)
- Assess bladder compliance, consider augment or diversion

Angioli et al. Critical Reviews in Oncology/Hematology; 48: 2003; 295.

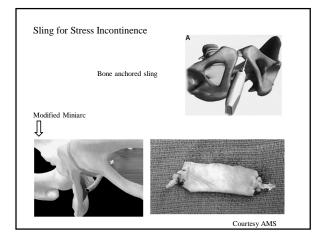


#### Non Hysterectomy Fistula

- Tend to be complex
- Understanding the underlying disease process and the surgical principles for repair are key
- Workup of bladder function / ureters follows the same principles as in hysterectomy fistula

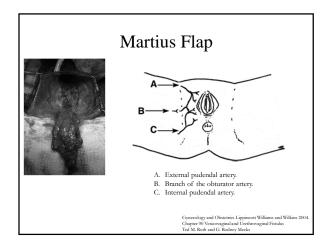
#### Spontaneous Fistula

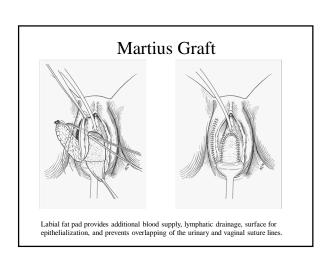


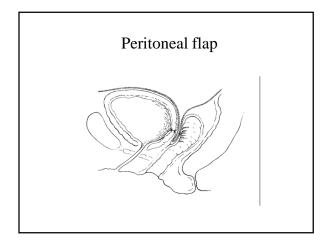


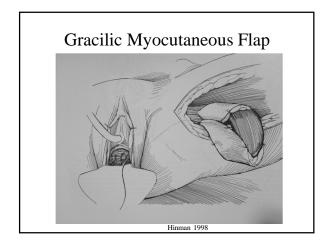
#### Surgical Therapy

- "First attempt is most likely to succeed"
- 1st attempts meet with 90% success
- · Factors that affect success
  - Etiology
  - Duration
  - Presence of necrosis or infection
  - Surgeon experience
    - -Dmchowski 2006









#### Rectovaginal Fistula

- 5-10 % of those with Crohn's will develop RVF (lower in UC)
- · Diverticulitis, Bartholin's, TB, Crytoglandular abscess
- LAR for Cancer: 1-10%
- Prolapse surgery with or without mesh/graft
- Mechanical Pessary, Sexual Practices, Trauma
- Cancer up to 6% after radiation
- Principals suggest diversion if radiation, inflammation

Champagne BJ, Surg Slin N Am 90 (2010) Venkatesh KS Dis Colon Rectum 1989 Tsang CBS, Surg Clinics N Am, 1997

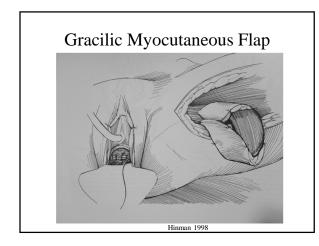
Treatment of recurrent rectovaginal/pouch-vaginal fistulas by gracilis muscle transposition — a single center experience

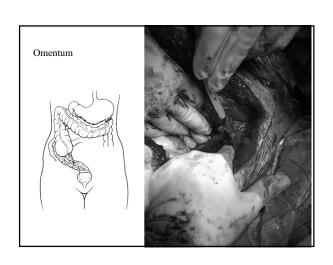
A. Troja\*, P. Käse, N. El-Sourani, H.-R. Raab, D. Antolovic
Journal of Visceral Surgery (2013), http://dx.doi.org/10.1016/j.jviscsurg.2013.08.002

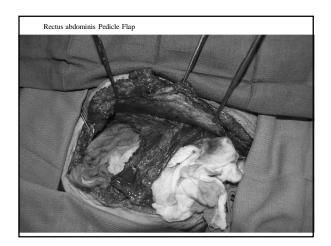
- 10 patients with recurrent GI-Vaginal Fistulas
  - 5 rectovaginal fistulas
  - 4 pouch-vaginal fistulas
    1 anovaginal fistula.
- Underlying disease:
   7 with Rectal cancer and XRT, 1 with Crohn's, 1 gynecologic surgery, 1 idiopathic
- Results:

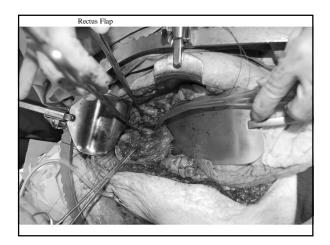
  - Follow-up 8 to 60 months.
    Recurrent rectovaginal fistula occurred in 4/10

  - Post-operative complications:
     1 perineal wound defect, 1 thigh hematoma









#### Non Hysterectomy Fistula

- Tend to be complex
- Understanding the underlying disease process and the surgical principles for repair are key
- Workup of bladder function / ureters follows the same principles as in hysterectomy fistula

#### **Identifying Patients With Vesicovaginal** Fistula at High Risk of Urinary Incontinence

Angela M. Bengtson, 14D, Dawn Kopp, MD, Jennifer H. Tang, MD, Ennet Chipungu, MBBS, Margaret Moyo, CNMT, and Jeffrey Wilkinson, MD

- 11 (3%) women had unsuccessful
- fistula closure. Of those with successful fistula closure (n5372), 85 (23%) experienced residual incontinence. A
- risk score cut point of 20 had sensitivity of 82% (95% confidence
- interval [CI] 72-89%) and specificity 63% (95% CI
- 57-69%) to potentially identify women with residual
- incontinence. In our population, the positive predictive value for a risk score cut point of 20 or higher was 43%
- (95% CI 36-51%) and the negative predictive value was 91% (95% CI 86-94%). Forty-eight percent of our study
- population had a risk score 20 or greater and, therefore, would have been identified for further intervention.

VOL. 128, NO. 5, NOVEMBER 2016 OBSTETRICS & GYNECOLOGY 945

20   1.00   1.		Bivariable Analysis	
\$5 do y surgery \$1.00 so \$0.00 years with finish \$1.00 (1.00 + 5.00 years with finish \$1.00 years with \$1.00 years years with \$1.00 years year	Preoperative Characteristic	OR (95% CI)	P
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\$ or less	Older than 50	3.20 (1.83-5.59)	<.01
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First varietiscend	Greater than 20	3.16 (1.48-6.73)	<.01
Fifty infered	HIV status		
MG (glam) - MG (gl			
Leaf Ban 2.5.0   1.00   2.32		0.74 (0.27-2.02)	.56
2.5.0 or greater or of port part of the property of the proper	BMI (kg/m²)		
0		0.98 (0.54-1.77)	.94
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Type 2         6.27 (2.5±15.49)         <            1.04 (8,75±14.14)         <			
Type 1			
Type   24.55 (0.04.62.72)			<.01
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None or mld		5.01 (3.07-8.16)	<.01
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Greater than 1.5 1.00	Urethrai length (cm)	1.00	
1.5 or less 5.07 (2.88-8.92) <			<.01

FEMALE UROLOGY

#### Which Surgical Technique Should be Preferred to Repair Benign, Primary Vesicovaginal Fistulas?

- The size of the fistules ranged from 15 to 20 mm, 'Mehmet Kamuran Bircan' The admission time was between 3 days and 21 years, and it was longer in less educated patients. The success
- rate was 96.4% (27/28) in the transabdominal transvesical group and 100% (25/25) in the transvaginal group (P =
- 1.00). The hospitalization period and complications were significantly reduced in the transvaginal group (P=.00
- and P = .004, respectively). No patients converted from a transvaginal to a transabdominal repair. There was only
- one recurrence in the transabdominal transvesical group. The patients were followed up for 1 year.
- Conclusion: Transvaginal repair of benign, primary VVFs is more advantageous than transabdominal transvesical
- repair. There was a significant decrease in the hospitalization period and complications rates using the transvaginal
- technique without tissue interposition.

ORIGINAL ARTICLE

Doctor! Will I be dry? Factors determining recurrence after vesicovaginal fistula repair

All Javed! Aziz Abdullah; Nuzhat Faruqui, Sher Shah Syed. Binat-ul-Mehdi, Abdul Jabbar Pirzada\*

6 40 patients

Overall success in 558 (87.2%) cases.

Multivariate analysis:

- Multiplicity (9-fold recurrence risk)

- Pre-operative size (10-fold recurrence risk)

- Pre-operative size (10-fold recurrence risk)

- Duration of the fistula (3-fold risk).

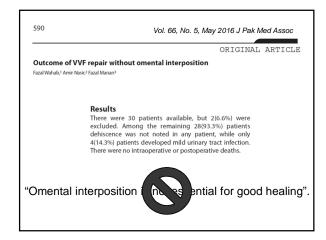
Interposition of flap and delayed reconstruction

(between 6 weeks and 1 year) was related to successful surgical outcome.

Age, parity, aetiology, route of repair and location of fistula were not significant (p>0.05 each) prognosic factors for recurrence.

Conclusion: Successful surgical repair of vesicovaginal fistula require careful evaluation of various factors, including number, size, previous attempts to surgical repair and duration of fistula.

J Pak Med Assoc Vol. 65, No. 9, September 2015



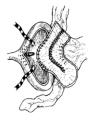
#### Tissue Loss

- In some cases pressure necrosis may destroy virtually the entire bladder, so that if the defect can be closed at all, the afflicted woman is left with a remarkably small (30 50 ml) bladder that compliance may be altered by the extensive fibrotic changes that often take place.
- To date there have been few urodynamic studies reported on patients who have undergone successful fistula closure

Schleicher DJ, OjengbedeOHA. International Urogynecology Journal 1993;4:262-5. Carey MP, Goh JT, Fynes MM, Murray CJ. Am J Obstet Gynecol. 2002 May;186(5):948-53.

#### Compliance/Capacity

- Decision-making regarding integration of augmentation into the repair of the fistula
- Diversion Catheterizable +/cystectomy



Tabakov ID, Slavchev BN. J Urol 171, 272-274, January 2004

### **Bladder and Urethral Diverticula**





Eric S. Rovner, M.D. Professor of Urology Medical University of South Carolina

#### No Relevant Disclosures

#### Bladder Diverticula

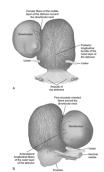
- Agenda:
  - Etiology and Pathophysiology
  - Diagnosis and evaluation
  - Management



#### Pathophysiology and Etiology

- Classification
  - Congenital (non-neurogenic, non-PBS/PUV, etc.)
    - Usually solitary
    - · Smooth walled bladder
    - Males (usually <10 y.o.)
    - Paraureteric (weakness in detrusor adjacent to ureter)
    - · Associated syndromes: Menkes, Williams, Ehlers-Danlos, etc
  - Acquired ("secondary")
    - BOO/NGB ("Hutch": paraureteric)/Post surgical
    - Often multiple, male
    - Associated with saccules, cellules, etc.

#### Histology/Anatomy



-Mucosa, +/- lamina propria, adventitia, capsule -Few if any detrusor fibers

-No contractile properties, empties poorly

Rovner, E.S.: Bladder and Female Urethral Diverticula In Wein,et al. (eds): Campbell's Urology, 10th edition

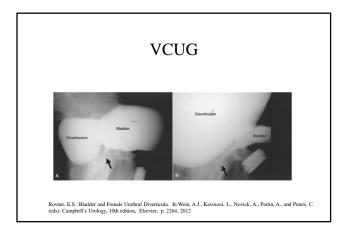
#### Diagnosis

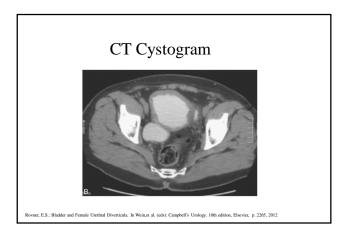
- Often asymptomatic
  - non-specific presentation
- Incidental finding
  - Found on evaluation for other sx, sign
    - Hematuria, UTI, LUTS/BOO, etc.
    - Imaging "incidental" finding

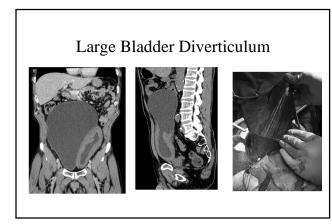
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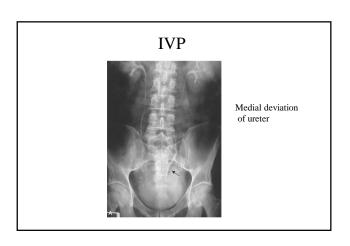
#### Evaluation

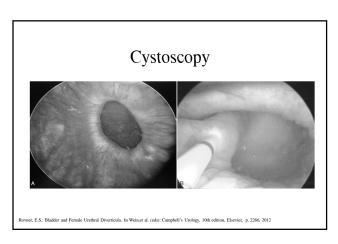
- History, PE, UA, cytology
- Radiographic: VCUG, CT, MRI, etc
- Cystoscopy
- Urodynamics











#### Urodynamics and Bladder Diverticula

- · Acquired BD often associated with BOO/NGB
- Necessary to identify the underlying abnormality
  - Beware
    - BD may act as "pressure sink" underestimating contractility
    - Artifactually elevated PVR (role for VUDS)
- Treat BD AND underlying abnormality
  - Sequential or concomitantly
    - If BOO treated and BD empties, then ?need for surgery

#### Indications for intervention

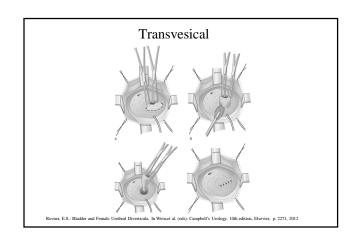
- Natural history unknown
  - ? Increased risk for malignancy (stasis)
- Symptoms/Signs attributable to tic
  - UT
  - Abdominal/Pelvic discomfort
  - LUTS
  - Malignancy
  - Hydronephrosis
  - Other



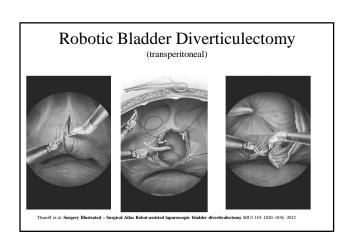
ovner, E.S.: Bladder and Female Urethral Diverticula. In Wein,et al. (eds): Campbell's Urology, 10th edition, E

#### Management

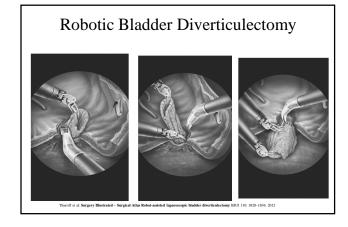
- -If Asymptomatic:
  - Observation/expectant management
    - -Surveillance (malignancy risk??)
- -If Symptomatic:
  - -CIC (?)
  - Endoscopic management
  - Surgical management
    - -Transabdominal
      - Open vs. minimally invasive
      - Extravesical vs. Intravesical vs. combined

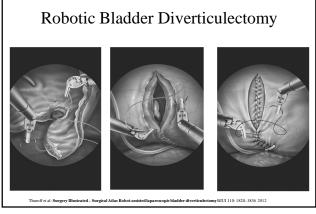


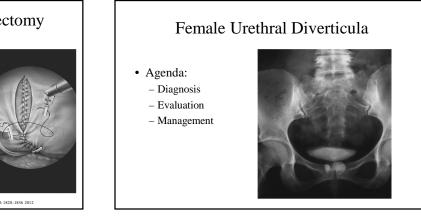
## Minimally Invasive • Laparoscopic • Robotic Thuroff et al: Surgery Illustrated - Surgical Atlas Robot-assisted laparoscopic bladder diverticalectumy BIUI 110: 1820-1836, 2012

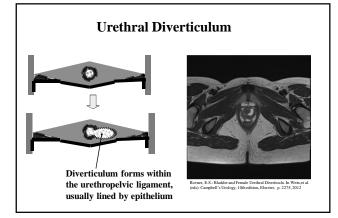


## Robotic Bladder Diverticulectomy Thuroff et al: Surgery Illustrated - Surgical Atlas Robot-assisted laparoscopic bladder diverticulectomy BJUI 110: 1820-1836 2012









## ".....found in direct proportion to the avidity with which it is sought"\* Davis, Te Linde, et al, JU 1958 @ Johns Hopkins: 1894-1955: 9 UD 1955-1956: 50 UD (development of PPU) \*Moore, JU 1952

**UD**: Prevalence

#### Urethral Diverticula: Prevalence

Overall: 0.6 – 4.7% of females (????)

- Depends on series
  - Primary vs. Tertiary care, GU vs. GYN, sx's, etc.
  - Autopsy: 3/500
  - ASx patients: 3/300 on PPU\*\*\*
  - 4.7% of ASx females screened for UD on admission for OB/GYN problems
  - Asymptomatic vs. symptomatic patients
    - Up to 40% of patients with LUTS suggestive of UD have UD\*\*
    - 4-20% of patients with UD are ASx at presentation
- Underdiagnosed?
  - Non-communicating UD\*

\*Daneshgari F et al. J. Urol. 1999 \*\*Stewart et al, BJU, 1981 \*\*\*Andersen, et al, J Urol 1967

#### Prevalence exaggerated ??

- · Recent study on UD incidence
  - Records of Rochester Epidemiology Project
    - Olmstead county 1980-2011
    - 26 new cases (Mayo: 142 cases)
    - Annual incidence = 17.9/1,000,000

El-Nashar SA et al:. IUJ, 2013

#### **UD**: Etiology (congenital vs. acquired)

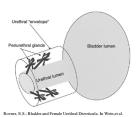
-Congenital

Rare reported cases in peds

-Acquired

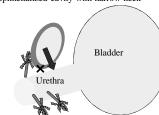
Paraurethral Glands (prostatic analogue)

- Drain into distal 1/3 of urethra
  - · Most distal are Skenes
- Largest and highest concentration of glands are located laterally and dorsolaterally
  - · Secretory, columnar epithelium
  - · Ductal/periductal inflammation common



#### Urethral Diverticula: Pathophysiology\*

- -Obstruction of paraurethral ducts/glands
- .....dilation
- -Abscess formation (?)
- -Rupture back into urethral lumen -Residual epithelialized cavity with narrow neck



#### Evidence for UD <u>origin in</u> <u>Paraurethral</u> glands

-UD located usually in

mid 1/3 of urethra Variable size,

shape and extension toward BN -Ostia located postero-

laterally (dorso-

-10% bilateral -Epithelium variable: columnar, transitional, cuboidal, or absent

\*Routh 1890

#### **UD:** Risk Factors/Associations

#### Historically:

1. Trauma: childbirth, multiparity

but up to 1/3 occur in nullips

2. Race: african americans up to 6 fold incidence

?but population bias at those reporting centers

3. Gonoccocal infection

but most culture out e. coli in urine

#### Urethral Diverticula: Diagnosis

(often missed)

#### History:

-often non-specific presentation over years

-irritative voiding symptoms, pain, UTI

(3 "D' s": Dysuria, Dyspareunia, post-void Dribbling)

#### Physical examination:

-tender anterior vaginal wall mass with urethral discharge upon palpation and stripping of anterior vaginal wall

#### **Imaging**

Endoscopy

+/- Urodynamics

#### Difficult Diagnosis

- Radiographic Diagnosis\*
  - 65% VCUG (30)
  - 11% Double balloon PPU (5)
  - 15% MRI/Ultrasound (7)
  - 9% incidentally found during surgery (4)

\*Romanzi, Blaivas: JU 164:428, 2000

BEWARE: prior periurethral bulking agents



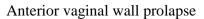


#### Periurethral Masses: Differential Dx

- Retrospective review
- 78 consecutive patients with periurethral masses
  - 84.6% UD
    - 3 with occult cancer
  - 4.1% vaginal leiomyoma
  - 3.8% vaginal cyst
  - 2.6% ectopic ureter
  - 3.8% other: Nabothian cyst, Sq. cell Ca, infected granloma

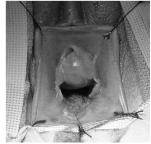
Flisser, A., Blaivas, J. et al, JU













Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein,et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2282, 2012

#### **Ectopic Ureter**





Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein,et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2282, 2012

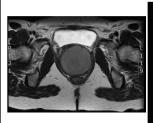
### Vaginal leiomyoma

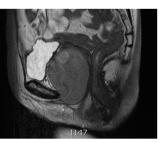




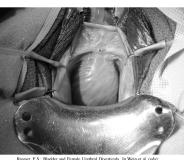
Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein,et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2282, 2012

#### Vaginal Leiomyoma





#### **Urethral Diverticulum**



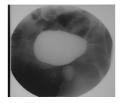
Rovner, E.S.: Bladder and Female Urethral Diverticula. In W Campbell's Urology, 10th edition, Elsevier, p. 2278, 2012

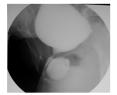
#### UD: complicating/co-existent conditions

- Tumors (<100 cases reported)
  - Malignant:
  - AdenoCa:46%
  - TCCa: 38% Sq. Cell Ca: 12%
- Benign: nephrogenic adenoma, endometriosis
- Incontinence: up to 57%
  - Differentiate from post-void dribbling
  - If true, bothersome SUI: Consider aPVS (NOT MUS)
- UTI's (may or may not resolve)
- Pelvic pain/dysparuenia (may or may not resolve)
- Stones (up to 10%)

66 y.o. with dysparuenia and UTI's





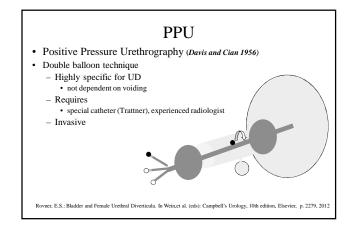


#### Urethral Diverticula (Imaging)

- Why image?
  - Confirm clinical diagnosis:
    - Skene's gland cyst, leiomyoma, prolapse, etc.
  - Anatomy
    - location
      - sphincter/bladder neck
    - size/complexity/urethral involvement
    - ostia

#### Urethral Diverticula

- PPU (Double balloon)
- VCUG
- · Transvaginal Ultrasound
  - operator dependent
  - images lack precise "surgical anatomy"
- MRI



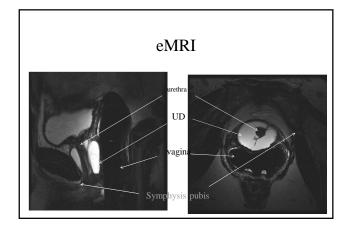
#### **VCUG**

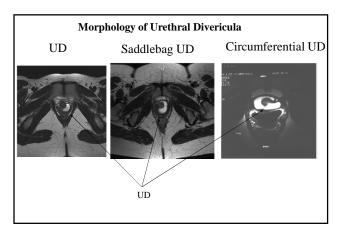
- Invasive, painful
- must void to image UD
- ostia must be patent to image UD
- poor stream will underestimate size, loculations(?)
- Utility
  - Readily available
  - Inexpensive



#### Urethral Diverticula and MRI

- Surface coil
  - Hricak, et. al., Radiology, 178:527, 1991 (9 patients)
  - Kim, et. al., AJR, 161:809, 1993 (16 patients)
  - Neitlich, et. al.., J. Urol., 159:408, 1998 (6 patients)
- Endoluminal coil (endovaginal, endorectal)
  - Siegelman, et. al., Radiographics, 17:349, 1997
  - Blander, Rovner, et. al., Urology, 53:818, 1999 (case report)
  - Blander, Rovner, et al, Urology 57: 660, 2001 (27 patients)





#### Endoscopy

- · Flexible cystoscopy
- Rigid with "female sheath"
- Assess:
  - Ostia (number, location, etc.)
  - Sphincter
    - bladder neck competence, etc.



#### Urodynamics/videourodynamics

- · Consider if:
  - Significant LUTS/UI
  - Differentiate between SUI and post void dribbling
  - Elevated PVR: BOO vs. detrusor underactivity

#### Management of UD

- Non-operative
  - Watchful waiting (Asymptomatic)
  - Antibiotic prophylaxis (if UTI)
  - Digital stripping of anterior vaginal wall
- · Operative
  - Endoscopic management
    - Spence-Duckett
    - Marsupialization
  - Excision and reconstruction (+/- sling)

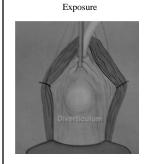
#### Excision of Urethral Diverticula

#### **Principles**

- -preservation of the periurethral fascia
  - -closure of dead space
  - -multi-layered closure
- -identify and excise the neck or ostia
- -remove epithelialized sac
- -preserve or create continence

#### **Operative Preparation**

- Proper consent:
  - Recurrence of symptoms/UD
  - Review complications (fistula, SUI, etc.)
  - +/- episiotomy, Martius flap
- Urine culture (antibiotics)
- Lone Star retractor, weighted speculum
- Loupes, headlight

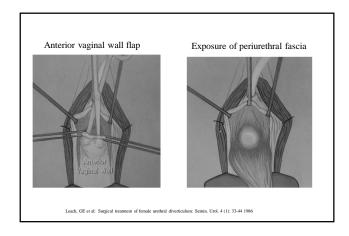


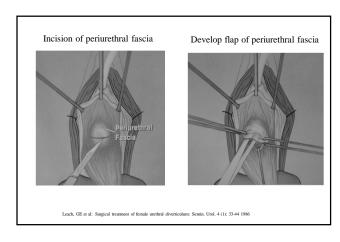


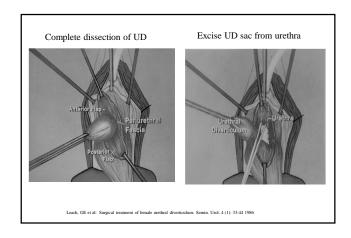


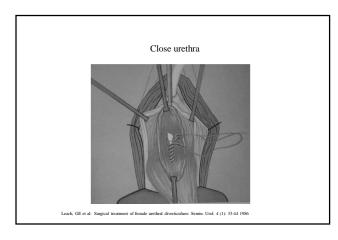
Leach, GE et al: Surgical treatment of female urethral diverticulum: Semin. Urol. 4 (1): 33-44 198

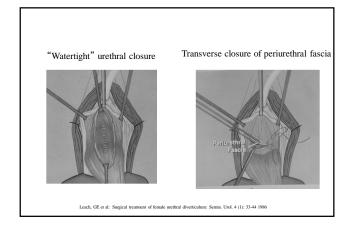
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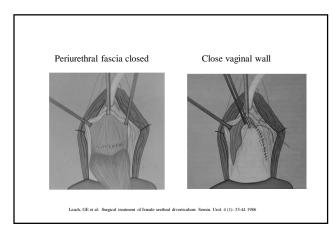












### Complications of Transvaginal Urethral Diverticulectomy (UD)

#### Complication (% Range of Reported Incidence)

Urinary incontinence (1.7%-16.1%) Urethrovaginal fistula (0.9%-8.3%)

Urethral stricture (0%-5.2%) Recurrent UD (1%-25%)

Recurrent urinary tract infection (0%-31.3%)

Other:

Hypospadias/distal urethral necrosis

Bladder or ureteral injury

Vaginal scarring or narrowing: dyspareunia, etc.

Rovner, E.S.: Bladder and Female Urethral Diverticula. In Wein,et al. (eds): Campbell's Urology, 10th edition, Elsevier, p. 2277, 2012

## Summary: Bladder and Urethral diverticula

- -Can be difficult diagnosis
- -Anatomy variable

BUT: anatomic problem=anatomic solution

-Primary treatment:

surgical excision and reconstruction



#### Non-Muscle Invasive Bladder Cancer

Angela B. Smith, MD, MS, FACS
Associate Professor
Department of Urology
University of North Carolina
Lineberger Comprehensive Cancer Center

#### **Disclosures**

- AHRQ K08 (research funding)
- PCORI (research funding)
- Photocure consultant (for consensus guidelines)

#### **Bladder Cancer Statistics**

- Incidence: ~81,190
  - » 75% NMIBC
  - » 20% MIBC
  - » 5% metastatic
- Prevalence: ~675,000
- 17,240 deaths annually

At a Glance

| Stational No. Control 2011 | Station | S

#### **Epidemiology**

- · Median age 72 years
- Male:Female 3:1
  - » 4th most common cancer in US men
  - » 12th most common cancer in US women
- · Racial predominance:
  - » Caucasians > African Americans > Hispanics > Asians
  - » Higher death rate among women and African Americans

#### **Risk Factors**

- Cigarette smoking
  - » Risk increases 2-6 times
- Pelvic radiation
  - » Prostate, rectal, cervical cancers
- Drugs
  - » Cyclophosphamide, ifosfamide, phenacetin
- Chronic cystitis
- » Schistosoma hematobium (bilharziasis)
   Environmental exposure
- » Aluminum, dyes, paint, textiles, petroleum, rubber
- Miscellaneous
  - » Arsenic, Balkan nephropathy (Aristolochia species)

#### **Genetics**

- <10% cases have family history
- Relative risk increases 2-fold with FH but non-hereditary
- · Lynch Syndrome II
  - » Defect in DNA mismatch repair
  - » Rare familial syndrome
  - » Predisposes to bladder and UTUC
- Polymorphisms in detoxification mechanisms contribute to higher susceptibility to environmental carcinogens
  - » Among smokers
  - » Glutathione-S-transferase M1 null genotype → higher risk

#### Prevention of bladder cancer

· Eliminate initiating risk factors

Smoking (33-50%) Occupational exposure (25-27%) Radiation Chemotherapeutic agents Catheters, foreign bodies

· Suppressing promotion in initiated cells

Diet Vitamins Oral agents

#### Chemoprevention

- High dose antioxidant vitamins have unclear benefit
  - » Vitamins A, B1, B2, B3, B5, B6, B12, C, D, E, folate, zinc
  - » May have a role for LG UC after BCG
  - » Potential hepatotoxicity of high doses of Vitamin A
- Fruit and vegetables **DECREASED** risk
- Fat and cholesterol INCREASED risk
- Non-chlorinated water > 6 cups/day DECREASED risk

#### Screening



- · Potential benefits of screening
  - » Easily performed
  - » Early detection
  - » Rarely indolent (found on autopsy)
- Screening not recommended by USPSTF (2011)
  - » Incidence 21/100,000 (0.02%)
  - » Not specific; increase burden with false +
  - » Heterogeneous nature of bladder cancer
- · Enrich the screened population
  - » Smokers?
- · Better screening tools beyond dipstick UA

#### Signs and Symptoms

- Intermittent gross painless hematuria (80%)
- Irritative voiding (20%)
- Mucosuria
- · Additional signs/symptoms rare
  - » Usually related to advanced cancer
  - » Not noted in NMIBC
- · Incidental diagnosis (imaging)



#### 2016 AUA/SUO Guidelines for NMIBC

#### 2007 Panel members

M.Craig Hall,M.D., Chair Sam S. Chang,M.D. Guido Dalbagni, M.D. Raj S. Pruthi,M.D. Paul F. Schellhammer, M.D. John D. Seigne, M.D. Eila C. Skinner, M.D. J. Stuart Wolf, Jr., M.D.



2016 Panel members Sam S. Chang, M.D., Chair Jim McKiernan, M.D., Vice Chair Steve Boorjian, M.D. Peter Clark, M.D. Sia Danshmand, M.D. Badri Konety, M.D. Raj S. Pruthi, M.D. Diane Quale, Patient Advocate Chad Ritch, M.D. John D. Seigne, M.D. Eila C. Skinner, M.D. Norm Smith, M.D.

#### **NMIBC DIAGNOSIS**

#### **Evaluation**

- · Imaging of Upper Tracts
  - » CT urogram, MRI, retrograde pyelogram, IVP
  - » Prior to TURBT preferred
- · Cystoscopic inspection of the bladder
- Transurethral Resection of Bladder Tumor (TURBT)
- · Additional considerations
  - » Enhanced cystoscopy (when available)
  - » Random biopsies
  - » Upper tract washes
  - » Prostate urethral biopsies
- · Urinary Cytology



#### **CT Urogram**

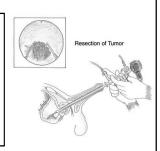




#### **TURBT**

- "Focal"
- "Targeted"
- "Personalized"
- "Single-port"
- "Natural orifice"
- "Scope"
- "No scalpel" technique "Minimally invasive"

Slide courtesy of S. Chang



#### **Complications of TURBT**

- · Urinary tract infection
- Bleeding (early or delayed)
- · Bladder perforation
  - » Associated with the obturator reflex
  - » Distinguish extra from intraperitoneal (intraop cystogram)
    - EP can be managed conservatively
    - IP (particularly if large) should be repaired





## TURBT: Experience Makes a Difference

- When compared to experienced surgeons, lesser experienced surgeons
  - » more likely to leave residual tumor (OR 7.3)
  - » more likely to lack muscle in the specimen (OR 8.5)
    - When detrusor muscle present residual tumor rate 20%
    - $\bullet\,$  BUT when detrusor muscle was  $\mathbf{absent}$  residual tumor rate  $\mathbf{51\%}$

Huang J et al, Urol Int 89 (2012)

#### Monopolar vs Bipolar Electrocautery

- Puppo et al assessed the safety of bipolar TURBT in 480 consecutive patients
  - » 2% rate of obturator nerve reflex
  - » 0.8% blood transfusion rate
  - » no cases of transurethral resection syndrome
  - » no thermal skin lesions

Puppo P et al, J Endourol, 23 (2009)

#### Monopolar vs Bipolar Electrocautery

- Randomized, single center trial examined 147 patients and found
  - No difference in:
    - Bleeding
    - · Obturator reflex
    - · Operative time
    - Hyponatremia
    - Complications



 The only advantage was decreased cautery artifact with bipolar

Venkatramani et al, J Urol, June 2014

#### **Cystoscopy and Biopsy**

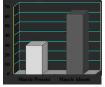
- Cold cup excisional biopsy with fulguration is acceptable for small papillary tumors
- Office laser or fulguration (without biopsy) could be considered for established low-grade small papillary lesions
  - » Studies ongoing to determine safety of active surveillance
- · Tumor in a diverticulum
  - » Ta disease can be safely removed if technically feasible
  - » T1 disease (particularly high grade) may be understaged
    - · Consider partial cystectomy/diverticulectomy if isolated
    - Consider random bladder biopsies of diverticular rim to assure cancer limited to diverticula

#### Importance of Re-TURBT

- Incomplete resection is likely a significant contributing factor to early recurrences, as tumors have been noted at the first follow-up cystoscopic evaluation in up to 45% of patients
- Repeat resection should be:
  - » Performed after an incomplete initial resection if feasible
  - » Considered for those with high risk HGTa tumors
  - » Performed for those with HGT1 disease

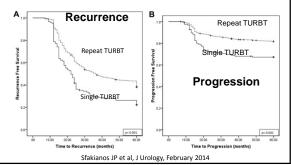
#### Why re-resect T1 disease?

- Understaging in about 30%
  - Greater (up to 50%) with no muscle in the specimen
- Patients w/ residual T1 (after presumed complete resection) have up to 80% chance of progression



Cookson MS, et al: J Urol 2001;166: 490

## Re-TURBT Decreases Recurrence and Progression

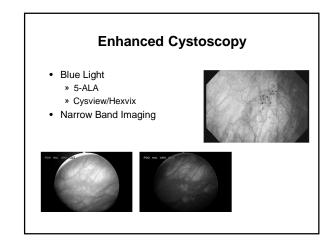


## Can re-TUR of T1 tumors select patients for immediate cystectomy?

- 352 T1 tumors evaluated by restaging TUR
- 58% (n = 203) had residual tumor on restaging including 92 (26%) with residual T1
- 82% patients with residual T1 cancer progressed to T2 compared to 19% with no or non-T1 tumor on re-TUR

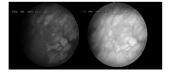
5 year progression probability Herr HW, et al. J Urol 2007;177(1);75-79

#### Can re-TUR of T1 tumors select patients for immediate cystectomy? 352 T1 TUR Ta/CIS (n=111) 58% (r restaging includii 82% p progre ith no or non-T 5 year progression probability Herr HW, et al. J Urol 2007;177(1);75-79



#### Fluorescence Cystoscopy

- Hexaminolevulinate or precursor 5-ALA causes porphyrins to accumulate in tumor cells
- · Porphyrins emit red color when exposed to blue light
- Instill 50cc into empty bladder and empty after 1 hour
- Perform white and blue (380-450nm) light cysto within 1 hour
- Use in OR with rigid cystoscopy (although flexible also recently approved)



#### **Blue Light Cystoscopy**

- A clinician should offer blue light cystoscopy:
  - » At the time of TURBT, to increase detection and decrease recurrence
    - Detection increased 20-30% papillary; 30-40% CIS
    - 12 month recurrence is absolute 10% less with BL
  - » In the presence of positive cytology with negative white light standard cystoscopy









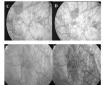
#### **Narrow Band Imaging**

- · Filters the white light into specific light wavelengths that penetrate only surface of human tissue and absorbed by hemoglobin:
  - » 415 (blue)
  - » 540 (green)
- · Capitalizes on peak absorption of hemoglobin
- · Accentuates vascular architecture of bladder tumors (compared to normal urothelium)
- · Does not require instillation agent
- · Avoids time delay and cost of agent



#### **Narrow Band Imaging**

- · A clinician may consider use of Narrow Band Imaging (NBI) to:
  - » increase detection and decrease recurrence
  - » Similar detection rates as BL but fewer studies; no randomized comparison



- Cauberg EC et al. Urol 76: 658, 2010
- superficial capillary network (brown)
- deeper vessel visibility: vessels are greenish-blue (cyan)

#### **Random Biopsies**

#### **APPROPRIATE**

- Cytology is positive yet no tumor is present
- Follow-up of prior CIS after treatment
- When contemplating partial cystectomy or bladder sparing approaches to rule out

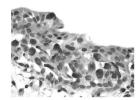
#### NOT APPROPRIATE

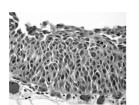
 Normal mucosa and tumor appears papillary, non-invasive with negative cytology

#### **Localizing Source of Positive Cytology**

- · Bladder (random biopsy and enhanced cysto)
- Upper tracts (selective cytology and imaging)
  - » Ureteroscopy if equivocal
- · Prostatic urethra
  - » Biopsy 5 and 7 o'clock, TURP
- · GYN source if workup completely negative
- If full workup negative, >80% likelihood cancer cells still coming from bladder

#### **Evaluate the Prostatic Urethra**





- Up to 40% of patients may have involvement of prostatic urethra in patients with invasive disease and can be easily missed
- Important predictor of invasive disease
- TUR biopsies at 5 and 7 o'clock adjacent to veru can help detect CIS

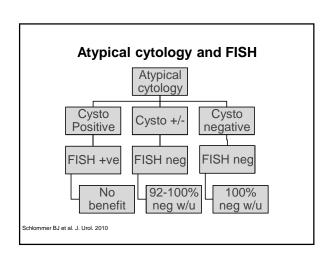
Wood D et al, J Urol, 1989; Huguet J, et al. Eur Urol. 2005;48:53-59

#### **Urine Markers**

- Commercial urine based markers for bladder cancer detection and/or surveillance
  - » Cytology
  - » BTA stat and TRAK
  - » NMP22 and BladderChek
  - » ImmunoCyt
  - » UroVysion FISH
  - » CertNDx
  - » Cx Bladder
- No study has evaluated effectiveness of urinary biomarkers to decrease mortality or improve outcomes compared with standard diagnostic methods

#### **Urine Markers**

- Given uncertainty in sensitivity these test CANNOT replace cystoscopy
- In general, lower specificity than cytology
- In surveillance, should <u>not</u> use urinary biomarkers in place of cystoscopy. (Strong Recommendation; Evidence Strength: Grade B)
- 10. History of low-risk cancer and a normal cystoscopy, should <u>not</u> routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)
- 11. May use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)



#### FISH and response to BCG

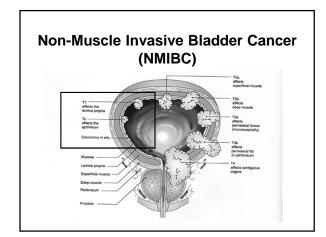
	Recurrence if post BCG FISH		% ≥T2
	Positive	Negative	
Kipp	100%	52%	58%
Whitson	89%	26%	
Mengual	52%	25%	10%
Savic	76%	26%	

Post BCG FISH predicts for recurrence and progression
 FISH useful if post BCG cytology equivocal

Whitson J, et al. BJU Int. 2009, Kipp et al. J. Urol. 2005 Mengual et al. Eur. Urol. 2007, Savic et al. Int. J. Cancer. 2009

#### Cytology

- · A normal result cannot rule out cancer
- 95% accurate if unequivocally positive for HG dysplastic cells
- False positives more common for "papillary clusters" especially with stones or instrumentation
- Ileal conduit or neobladder cytology accurate if positive but pathologist needs to know it is from a bowel segment
- Also difficult to evaluate cytology after radiation or intravesical chemotherapy (bottom line- communicate to your cytopathologist)



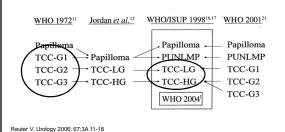
S	Staging of primary tumors (T) in blade	der cancer
TX	Primary tumor cannot be assessed	
Ta	Noninvasive papillary carcinoma	
Tis	Carcinoma in situ (CIS)	
T1	Tumor invades lamina propria	
T2	Tumor invades muscularis propria	
T2a	Tumor invades superficial muscularis phalf)	propria (inne
T2b	Tumor invades deep muscularis propris	a (outer half
Т3	Tumor invades perivesical tissue/fat	
ТЗа	Tumor invades perivesical tissue/fat mi	icroscopical
T3b	Tumor invades perivesical tissue fat ma (extravesical mass)	acroscopica
T4	Tumor invades prostate, uterus, vagina or abdominal wall	, pelvic wal
T4a	Tumor invades adjacent organs (uterus prostate stoma)	, ovaries,
T4b	Tumor invades pelvic wall and/or abdo	minal wall

#### **Staging**

American Joint
Committee on Cancer
(AJCC), also known as
the Tumor-NodeMetastases (TNM)
classification. Clinical
stage reflects the
histologic findings at
TURBT; the clinician's
physical exam, including
bimanual exam under
anesthesia; and findings
on radiologic imaging.

Edge 2010

## World Health Organization (WHO) Classification of Urothelial Neoplasms



#### Grading

2004 World Health Organization/ International Society of Urologic Pathologists:
Classification of Non-muscle Invasive Urothelial Neoplasia\*\*

Hyperplasia (flat and papillary)

Reactive atypia

Atypia of unknown significance

Urothelial dysplasia

Urothelial CIS

Urothelial papilloma

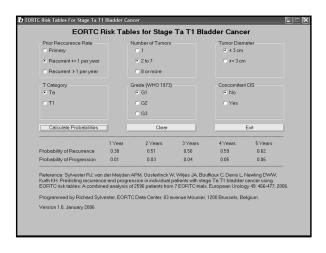
Papillary urothelial neoplasm of low malignant potential

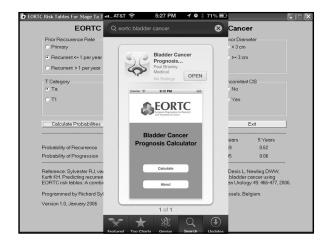
Non-muscle invasive low-grade papillary urothelial carcinoma

Non-muscle invasive high-grade papillary urothelial carcinoma

#### **Risk Stratification**

- EORTC and CUETO risk calculators
- · Limited by lack of applicability to current populations
  - » Few patients received BCG maintenance, re-staging TURBT, or post-operative mitomycin C.
- EORTC uses 1973 WHO grading system
- Does not incorporate prior use of BCG or treatment
- C-index (0.5 = coin flip; higher is better)
  - » EORTC = 0.66 / 0.75
  - » CUETO = 0.64 / 0.70





#### **AUA/SUO Risk Stratification**

Low Risk	Intermediate Risk	High Risk	
LG <sup>a</sup> solitary Ta ≤ 3cm	Recurrence within 1 year, LG Ta	HG T1	
PUNLMP <sup>b</sup>	Solitary LG Ta > 3cm	Any recurrent, HG Ta	
	LG Ta, multifocal	HG Ta, >3cm (or multifocal)	
	HG <sup>c</sup> Ta, ≤ 3cm	Any CIS	
	LG T1	Any BCG failure in HG patient	
		Any variant histology	
		Any LVI <sup>d</sup>	
		Any HG prostatic urethral	
		involvement	

 At the time of each occurrence/recurrence, assign a clinical stage and classify a patient accordingly as "low-," "intermediate-," or "high-risk." (Moderate Recommendation; Evidence Strength: Grade C)

#### **Histology - Conventional**

- 90-95% urothelial carcinoma
- 5% squamous cell carcinoma
- 0.5-2% adenocarcinoma
  - » Usually arise from urachus or trigone
  - » Can be prevalent among patients with bladder exstrophy
  - » Many have history of long-term inflammation/infection
  - » Non-urachal adenocarcinoma should undergo colonoscopy
    - · Distinguish from extension of colorectal primary

#### **Variant Histology**

- At TURBT, 86% (vs. 53%) with variant histology present with MIBC
- At cystectomy, 64% (vs. 34%) with variant histology with pT3-T4
- Micropapillary
  - » Unusual variant of UC but particularly resistant to BCG
  - » Early cystectomy preferred
- Plasmacytoid and Nested variants
  - » Aggressive
- » Cystectomy preferred
- Small cell (neuroendocrine)
  - » Stains with synaptophysin, neuron specific enolase, chromogranin
  - » Treat with upfront chemotherapy: platinum + etoposide
- Sarcomatoid
- » Treat with upfront cystectomy
- Carcinosarcoma
  - » Treat with upfront cystectomy



Small Cell

#### Variant Histology: From the Guidelines

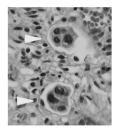
- · Pathologists need to report LVI and variant histologies
- 6. An experienced GU pathologist should review variant or suspected variant histologies (Moderate Recommendation; Evidence Strength: Grade C)
- 7. If a bladder sparing approach is considered, should perform a restaging TURBT within 4-6 weeks. (Expert Opinion)
- Due to high rate of upstaging, clinician should consider offering initial radical cystectomy. (Expert Opinion)

#### Impact of LVI on T1

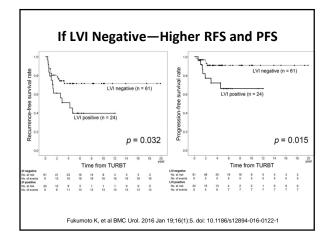
- Small study of 116 T1 patients
- LVI in multivariate analysis
  - » In all patients, associated with stage progression (HR = 4.0)
  - » In patients treated with BCG, associated with:

• Tumor recurrence (HR = 2.19)

• Stage progression (HR = 3.76)

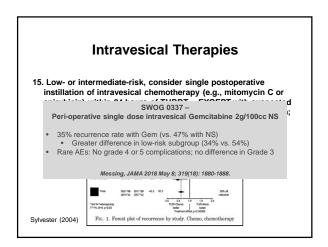


Fukumoto K, et al BMC Urol, 2016 Jan 19:16(1):5, doi: 10.1186/s12894-016-0122-1



#### NMIBC TREATMENT

# Intravesical Therapies 15. Low- or intermediate-risk, consider single postoperative instillation of intravesical chemotherapy (e.g., mitomycin C or epirubicin) within 24 hours of TURBT – EXCEPT with suspected perforation or extensive resection (Moderate Recommendation; Evidence Strength: Grade B) \*\*Total Control of the Control of th



#### **Intravesical Therapies**

- 16. <u>Low-risk</u> should not administer induction intravesical therapy. (Moderate Recommendation; Strength of Evidence Grade C)
- 17. <u>Intermediate-risk</u> *consider* administration of a 6 week induction intravesical chemotherapy or immunotherapy. (Moderate Recommendation; Evidence Strength: Grade B)
- High-risk patient with CIS, high-grade T1, or high-risk Ta, should administer 6-week induction course of BCG. (Strong Recommendation; Evidence Strength: Grade B)

#### **Intravesical Chemo Mechanisms**

- · Mitomycin
  - » Bioreductive alkylating agent that crosslinks DNA
- Anthracyclines (doxorubicin, epirubicin, valrubicin)
  - » Topoisomerase inhibitor and DNA intercalator
- Thiotepa
  - » Alkalating agent
- Gemcitabine
  - » Pyrimidine analog and incorporated into DNA/RNA
- Taxanes (docetaxel, paclitaxel)
  - » Microtubule superstabilizing agent

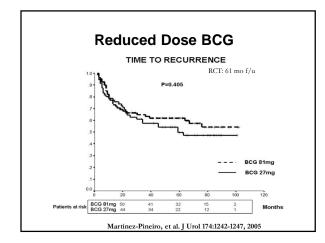
#### Intravesical BCG

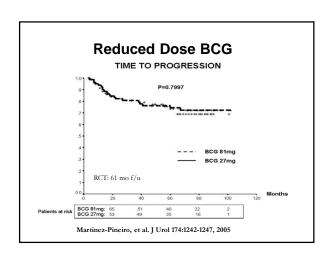
- Induction: weekly x 6 (5/6 considered adequate)
  - » Wait 2-6 weeks after TUR to start (or bleeding resolved)
- Maintenance: weekly x 3
  - » SWOG protocol 3, 6, 12, 18, 24, 30, 36 months
  - » 1 year full dose intermediate risk
  - » 3 year full dose high risk
- Dose
  - » May be reduced by 1/2 to 1/3 for tolerance
- Mechanism
  - » Th1 cellular immune response
  - » Increases IL-2, IL-12, IFN-gamma, TNF
  - » Decreases IL-10 and IL-4

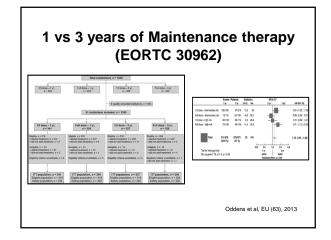
#### **Guidelines: BCG**

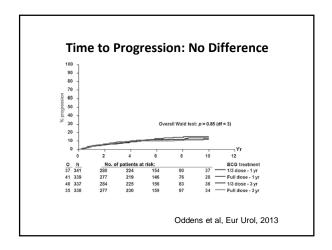
- · Insufficient evidence to recommend one strain of BCG
  - Several small studies suggest that different strains may have different efficacies
- · Insufficient evidence to prescribe a particular BCG strength
  - . EORTC and CUETO studies
  - For lower-risk patients, no difference in recurrence free survival between full or 1/3 dose at 1 or 3 years of maintenance
- There is insufficient evidence to recommend using BCG in combination with other intravesical agents (at this time...)
  - Ongoing trials currently examining synergistic combinations

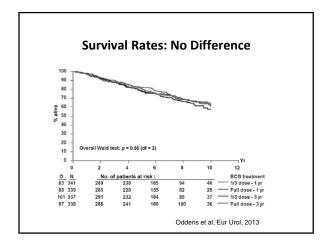
Rentsch 2014; Oddens 2013; Houghton 2013











#### EORTC-GU Cancers Group: Conclusions

- No differences in progression or survival rates in any of the arms
- No difference in morbidity between 1/3 and full dose arms
- Subgroup analysis
  - Intermediate risk: no difference 1 vs. 3 years
  - High risk: 3 years associated with ↓ recurrence

Oddens et al, Eur Urol, 2013

#### **Intravesical Maintenance Therapy**

- Intermediate-risk who completely responds to induction BCG, a clinician may utilize maintenance therapy. (Moderate Recommendation; Evidence Strength: Grade C)
- 20. <u>Intermediate-risk</u> who completely responds to induction BCG, should consider maintenance BCG for one year, as tolerated. (Moderate Recommendation; Evidence Strength: Grade C)
- 21. <u>High-risk</u> who completely responds to induction BCG, should continue maintenance BCG for three years, as tolerated. (Moderate Recommendation; Evidence Strength: Grade B)

#### **Defining BCG Unresponsive Disease**

- 6 month mark is important
- T1 disease
  - » Persistent disease within 6 months after receiving at least 5/6 BCG doses
- · CIS or Ta HG disease
  - » Failed two prior BCG courses (5/6)
  - » 5/6 induction; 2/3 maintenance
  - » Progression to T1 at 3 months
- Consider upper tracts and prostatic urethra when patients are not responding (e.g. + Cytology only)

#### **BCG** Relapse

- 22. Intermediate- or high-risk with persistent or recurrent disease or positive cytology following intravesical therapy, should consider performing prostatic urethral biopsy and an upper tract evaluation prior to administration of additional intravesical therapy. (Conditional Recommendation; Evidence Strength: Grade C)
- 23. In an intermediate- or high-risk with persistent or recurrent Ta or CIS disease after a single course of induction intravesical BCG, should offer a second course of BCG. (Moderate Recommendation; Strength of Evidence C)
  - » 50% patients with persistent/ recurrent NMIBC following first induction course of BCG respond to a second course of BCG

#### **BCG** Relapse

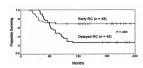
- 24. In patient fit for surgery with <u>recurrent HG T1</u> after a single induction BCG, should offer <u>radical cystectomy</u>. (Moderate Recommendation; Evidence Strength: Grade C)
- 25. A clinician <u>should not prescribe additional BCG if patient is intolerant or has recurrence</u> on TURBT of high-grade, non-muscle-invasive disease and/or CIS within 6 months of 2 induction courses of BCG or induction BCG plus maintenance. (Moderate Recommendation; Evidence Strength: Grade C)
- 26. With persistent or recurrent intermediate- or high-risk NMIBC who is unwilling or unfit for cystectomy following two courses BCG, a clinician may recommend <u>clinical trial</u> enrollment. May offer intravesical chemotherapy when clinical trials are unavailable. (Expert Opinion)

### Intravesical options in BCG-unresponsive disease

- Medically fit → Cystectomy
- · What if medical unfit or refuse
  - » Clinical Trial
  - » Docetaxel (intravesical)
  - » Gemcitabine + Docetaxel (sequential)
  - » (Valrubicin)
  - » (Gemcitabine)

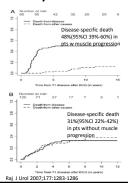
#### **Role of Cystectomy**

- Early, high-risk recurrences are at significant risk of progression; salvage intravesical therapies have poor success rates.
- Rationale for "early" cystectomy:
  - » Understaging (50% T1 are upstaged to >=T2 at cystectomy
  - » Significant "late" failure rate
  - » Potential survival benefit from avoiding delay of cystectomy



#### **Waiting Until Progression May Prove Fatal**

- A significant number of patients progress to detrusor muscle invasion
- Waiting for muscle invasion results in worse outcome supporting the role of early cystectomy in a select group of patients



#### Role of Cystectomy

- Ta low- or intermediate-risk disease, a clinician should not perform radical cystectomy until bladder-sparing modalities (staged TURBT, intravesical therapies) have failed. (Clinical Principle)
- 28. High-risk who is fit for surgery with persistent HG T1 disease on re-TUR, or T1 tumors with CIS, LVI, or variant histologies, should consider initial radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)
- 29. In high-risk with persistent/recurrent disease within one year following treatment with two inductions of BCG or BCG maintenance, should offer radical cystectomy. (Moderate Recommendation; Evidence Strength: Grade C)

#### **NMIBC FOLLOW-UP**

#### Risk-Adjusted Surveillance: Low Risk

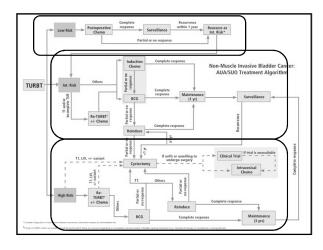
- First surveillance cystoscopy within 3-4 months
- Subsequent surveillance cystoscopy 6-9 months later
- · Annually thereafter
- Surveillance after five years in absence of recurrence based on shared decision-making
- No need for routine cytology or upper tract imaging
- In-office fulguration an alternative to resection under anesthesia for small sub-centimeter papillary recurrences

#### Risk-Adjusted Surveillance: Intermediate Risk

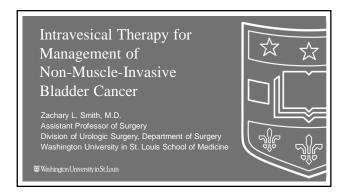
- First surveillance cystoscopy within 3-4 months
- Subsequent surveillance cystoscopy every 3-6 months for 2 years
- Then 6-12 months for years 3 and 4
- Annually thereafter
- Upper tract surveillance imaging every 1-2 years

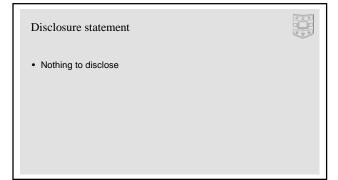
#### Risk-Adjusted Surveillance: High Risk

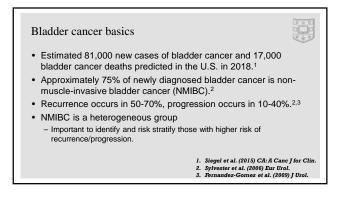
- First surveillance cystoscopy within 3-4 months
- Subsequent surveillance cystoscopy every 3-4 months for 2 years
- Then every 6 months for years 3 and 4
- Annually thereafter
- Upper tract surveillance imaging every 1-2 years

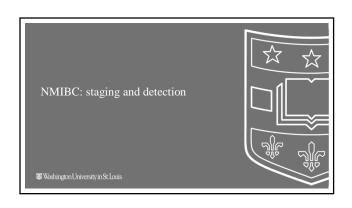


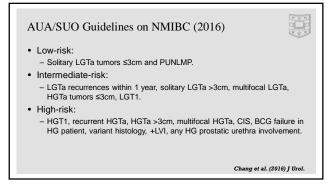


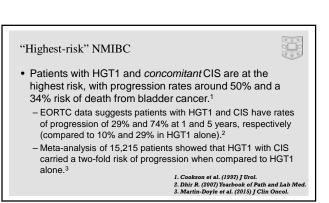












#### Role of repeat TURBT



- Up to 77% have residual tumor and 15-29% upstaged. <sup>1,2</sup>
  - Up to 50% upstaged in HGT1 patients when muscle not in original specimen.
  - Change in management in 1/3 patients.
- Re-TURBT reduces the frequency of early tumor recurrences and is thought to improve PFS.1,2
- Pathology on re-TURBT can be utilized as a prognostic indicator.
- Residual HGT1 at re-TURBT associated with increased risk of recurrence and progression.2
  - 2-year RFS only 26%.3
  - 23-82% risk of progression to MIBC (vs 6-19% without HGT1 on re-TURBT). 3.4
     3.7ae et al. (2017) PLoS ONE.
     3.6ae et al. (2015) BJI Int. 4.
     4.6ae et al. (2015) BJI Int. 4.

#### Blue-light cystoscopy



- Recurrence rates of NMIBC (all path) after white light cystoscopy (WLC) re-TURBT are 41%, 61%, and 73% at 2, 12, and 36 months.<sup>1</sup>
  - WLC detection of CIS can be as poor as 61%.
- Due to the high rates of recurrence and upstaging seen on WLC re-TURBT, new techniques have emerged→ blue light cystoscopy (BLC).
- Meta-analysis of RCTs: BLC with 5-aminolevulinic acid (5-ALA) or hexaminolevulinate (HAL) improves detection rate of CIS to ~90%.2

  - HAL (Cysview®) was approved by the FDA in 2010.
     Meta-analysis of BLC with HAL associated with improved detection rates of Ta, T1, and CIS (decreased recurrence at 12 months; 35% vs 45%).<sup>3</sup>
- NB: while BLC associated with improved RFS at 1 and 2 years, progression to MIBC not improved.4
  - 1. Daniltchenko et al. (2005) J Urol. 3. Burger et al. (2013) Eur Urol. 2. Grossman et al. (2007) J Urol. 4. Yuan et al. (2013) PLoS ONE.



#### Intravesical treatments: the basics



- · Delivery of medication directly to the site of the tumor
  - Minimizes systemic exposure
- Held in the bladder for as long as tolerable (ideally 2 hrs)
- Increased concentration by decreasing urine production
- Done in absence of bladder perforation and/or UTI
- Concepts:
  - Perioperative vs induction vs maintenance
  - Chemotherapy vs immunotherapy
  - Treatment vs prophylaxis

#### Intravesical treatments: the basics

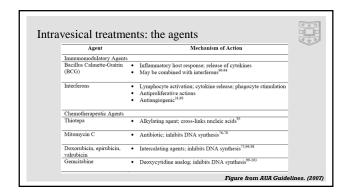


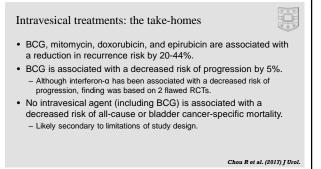
- · Who is a candidate?
  - AUA/SUO low-risk
    - Perioperative
  - AUA/SUO intermediate-risk
  - Induction +/- maintenance - AUA/SUO high-risk
    - · Induction +/- maintenance
  - MIRC?
    - · NMIBC recurrence after bladder preservation therapy

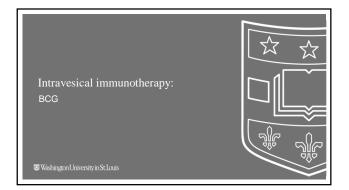
#### Intravesical treatments: the agents



- Chemotherapy
  - Mitomycin C, doxorubicin, epirubicin, valrubicin , gemcitabine, thiotepa, docetaxel, paclitaxel
    - · Combination: gemcitabine/docetaxel
- Immunotherapy
  - BCG, interferon-α, ?PD-1/PD-L1
    - Combination: BCG/interferon







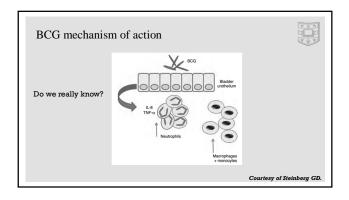
Immune system and the bladder: a primer

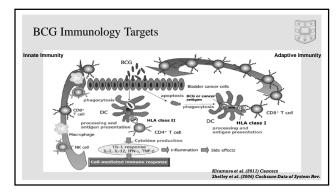
• PAMPs → TLR2 on tissue-resident macrophage → cytokines and chemokines

- Urothelial cells → secrete type I IFN (alpha and beta)

- Macrophages → engulfs pathogens → cytokines and chemokines

• Th1 response vs Th2 response





#### History of BCG



- 1929 Autopsy study: lower frequency of cancer in patients with active/healed TB
- 1950s (Old et al) Mice infected with BCG show resistance to tumor transplant
- 1970s (Zbar et al) delayed hypersensitivity rxn to BCG caused tumor inhibition
- 1975 (deKernion et al) treated melanoma of bladder with intravesical BCG
- 1976 (Morales et al) first successful use of intravesical BCG for non-invasive UC

  - Devised original protocol for induction:
     6 doses: Frappier strain packaged in 6 vials
     120 mg/dose: tolerated via intradermal route
     Weekly instillation: adverse effects <1 week
- 1978 (Morales et al) 7/10 patients exhibit tumor response in bladder
- Two RCTs, SWOG (Lamm) and MSKCC, confirmed reduced tumor recurrences compared to TURBT alone
- 1990 FDA approved intravesical BCG

Herr et al. (2008) J Urol. Agarwal PK. NIH/NCI

#### **BCG**



- · BCG is the gold standard adjuvant treatment for patients with HR
- BCG is used as the predominant (>2:1 majority) intravesical agent in North America, even in low/intermediate risk bladder cancer.
- · Numerous studies demonstrate reduction in both recurrence and progression.1-3
- · Numerous studies have supported the efficacy of intravesical BCG as a treatment for CIS.
  - Lamm et al reviewed 34 series (1,354 patients) and noted an average CR rate of 72% in CIS patients.4

#### BCG maintenance



- SWOG 8507<sup>1</sup> compared induction vs induction + 3 years of maintenance.
  - 3 weekly instillations at 3, 6, 12, 18, 24, and 36 months.
  - Overall CR rate increased from 56% to 82% with additional maintenance
- However, the vast majority did not complete the 3-year schedule due to toxicity.
- EORTC-GU Cancers Group Randomized Study<sup>2</sup> compared 1/3D vs FD and 1 yr vs 3 yr
  - Intermediate-risk: FD-1 yr equal to FD-3 yr
  - High-risk: FD-3 yr has lower recurrence rate (similar progression/death)
- The AUA recommends induction BCG followed by 1-3 years of
- maintenance, depending on risk.3
  - Lamm et al. (2000) J Urol.
     Oddens et al. (2013) Eur Urol.
     Chang et al. (2016) J Urol.

#### BCG treatment protocol





#### BCG failure



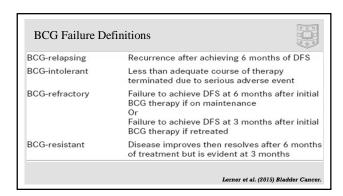
- · Despite aggressive treatment with BCG...
  - ~20-65% (avg ~40%) recur
  - ~20-40% progress
  - And manysome won't tolerate treatment.
- ~15,000 patients per year are deemed a BCG "failure" to some degree

#### BCG failure



- · Those that recur after BCG require second line therapy, most of which—outside of radical cystectomy—are not effective.
- · However, there is wide heterogeneity among BCG failures:
  - Papillary vs CIS, LG vs HG, number of failed courses, time of failure, failure during maintenance
  - Even the terms BCG refractory/resistant/failure have different meanings to different people

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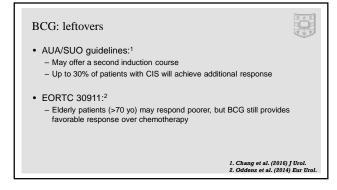


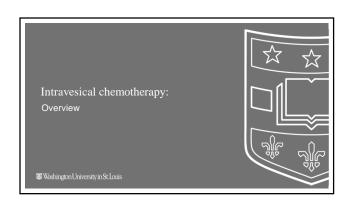
### BCG-unresponsive: HR NMIBC unlikely to benefit from further intravesical BCG



- Patients that don't respond to intravesical BCG and have a new or persistent HG recurrence at 6 months after initiation of BCG
- Have received at least two courses of BCG
- The "5+2" rule: at least 5/6 + at least 2/3
- Relapse within six months of last instillation with HG NMIBC
- All papillary NMIBC should be completely resected prior to BCG

Lerner et al. (2015) Bladder Cancer.





#### Intravesical chemotherapy

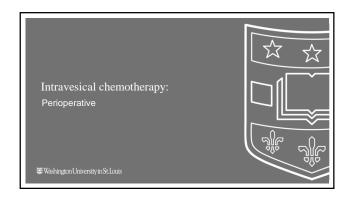


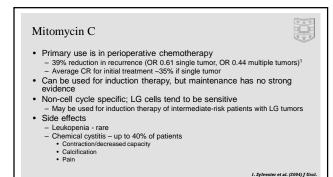
- Historically, when compared to BCG, intravesical chemotherapy has not been highly efficacious
- · Much of this is secondary to the high efficacy of BCG
- Chemotherapy must be better than BCG to be front-line (which it is not)
- Therefore, it is often second-line treatment
  - Second-line treatment by nature will have worse outcomes

#### Intravesical chemotherapy: when and why?



- · Perioperative treatment
  - Mitomycin C
- Gemcitabine
- Induction +/- maintenance
- Primary
  - Mitomycin C
- BCG-unresponsive
- Mitomycin C
- Valrubicin
- Gemcitabine/docetaxel





Gemcitabine

Can be used in perioperative setting

More readily available, less costly, less toxic than mitomycin C

SWOG S0037:

- 4-yr recurrence 35% vs 47% with saline (HR 0.66, p<0.001)

For low-risk, 34% vs 54% (HR 0.53, p<0.001)

Direct comparison to mitomycin C not performed due to large sample size requirement

New standard of care for perioperative chemo?

Poor utilization

• Despite supportive evidence, use remains low in U.S. (1-16%)¹

- Access?

- Cost?

- Unknown histology?

• Unnecessary treatment for some

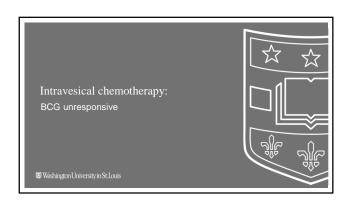
- Real benefit?

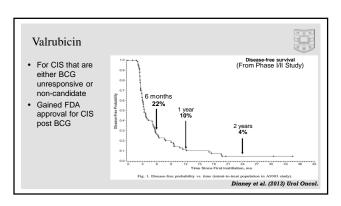
• Randomized study comparing postoperative saline CBI to mitomycin²

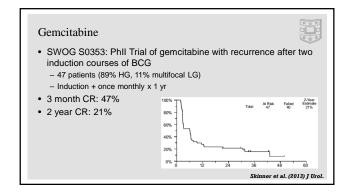
- No difference in progression, time to recurrence, or 5-year RFS

• May improve with adoption of gemcitabine

1. Cookson et al. (2012) [ Urol. 2. Onishi et al. (2017) B[U Int.

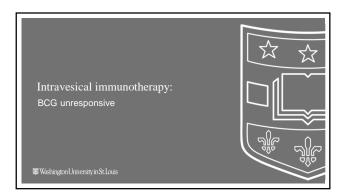




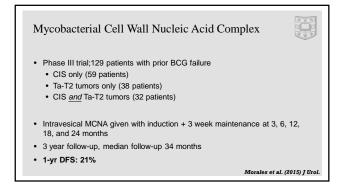


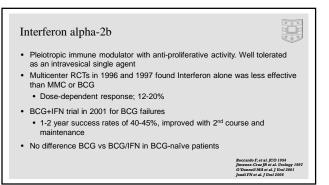
## Gemcitabine/docetaxel • 33 patients, full induction course • Median DFS: 6.5 mos (42% 1-yr and 24% 2-yr DFS). • Median HG-RFS: 17.1 mos (56% 1-yr and 42% 2-yr HG-RFS). • Median HG-RFS (among pts with HG path): 15.7 mos (51% 1-yr HG-RFS and 34% 2-yr HG-RFS). • No significant predictors for HG-RFS or DFS. • 5 LG recurrences, and 16 HG recurrences, with 6 progressions among these. 7 (21%) underwent RC at a median of 14.9 mos.

Milnar et al. (2017) Presented ASCO.



## Intravesical immunotherapies • Mycobacterial Cell Wall Nucleic Acid Complex (MCNA) • Interferon-α2b (IFN) • Recombinant adenovirus-mediated IFN-α2b (Instiladrin)





#### Instiladrin (rAd-IFN/Syn3)



- Syn3 is a novel medium that facilitates intravesical adenovirus vector mediated transduction of IFN- $\alpha$
- Open Label Phase I trial assessed 17 patients
  - Detectable urine IFN-α >10 days following transduction
  - Minimally detectable serum IFN-α (peaked in 24 hours)
  - No Grade 3+ adverse events
  - 40% patients with complete response

J Urol. 2013 September; 190(3): 850-856.

#### Instiladrin (rAd-IFN/Syn3)



- Phase II open label study Completed
- BCG-unresponsive NMIBC population (n=40)
- 35% 1 year RFS (50% RFS in papillary; 29% RFS in CIS)
- · Phase III open label study Ongoing
  - · Plan to enroll 135 patients
  - Single intravesical instillation, further maintenance doses given after 3, 6, 9 month surveillance cystoscopies
  - Primary outcome: 12 month complete response

#### Novel intravesical immunotherapies



- Vaccinia Virus
- Vicinium (VB4-845)
- CG0070 Oncolytic Adenovirus
- Gp96 (Heat Biologics ImPACT)
- ALT-803 (IL-15 superagonist)
- Imiquimod (TMX-101)

#### A First in Human Phase 1 Study of CG0070, a GM-CSF Expressing Oncolytic Adenovirus, for the Treatment of Nonmuscle Invasive Bladder Cancer

James M. Burke,\*,† Donald L. Lamm,‡ Maxwell V. Meng,§ John J. Nemunaitis,¶ Joseph J. Stephenson, James C. Arseneau,‡ Junko Aimi, Seth Lerner, Josey W. Yeung,§ Troy Kazarian,¶ Daniel J. Maslyar§ and James M. McKiernan

- CG0070 Oncolytic Adenovirus targeting RB defective pathway mutations
- Phase I trial assessed 35 patients
  - Open Label, dose escalation



THE JOURNAL OF UROLOGY® ol. 188, 2391-2397, December 2012

#### A First in Human Phase 1 Study of CG0070, a GM-CSF Expressing Oncolytic Adenovirus, for the Treatment of Nonmuscle Invasive

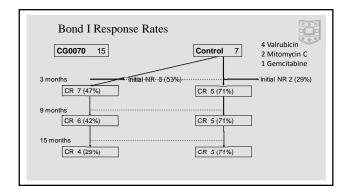
James M. Burke,\*,† Donald L. Lamm,‡ Maxwell V. Meng,§ John J. Nemunaitis,¶ Joseph J. Stephenson, James C. Arseneau,‡ Junko Aimi, Seth Lerner, Alex W. Yeung,§ Troy Kazarian,∥ Daniel J. Maslyar§ and James M. McKiernan

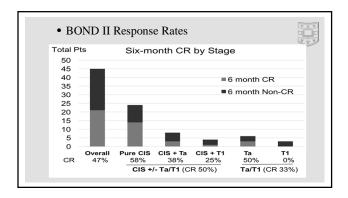
٠. ١	Yeung,s Troy Kazarian, Daniei J. Masiyars and James M. McKiernan			
	Subgroups Examined	N	Complete Response "CR" Rate @ 3 months (CR/n)	Median Duration of Complete Response (months)
	All Patients	35	48.6% (17/35)	10.4
	Multiple Dose Subgroups combined (4 weekly + weekly X 6)	22	63.6% (14/22)	16.1
	4 Weekly		53.9% (7/13)	15.3
	Weekly X 6	9	77.8% (7/9)	36
	pRb( ~and high) in Multiple Dose Subgroups Combined	11	81.8% (9/11)	25
	pRb ( ~and high) in Weekly X 6	5	100% (5/5)	Not Reached

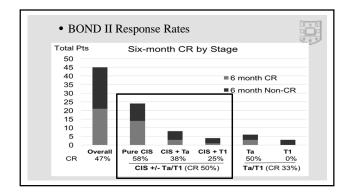
#### CG0070 Phase III Trials



- Bond I Study Design
  - CIS and CIS with Ta and/or T1 disease
  - Randomized 2:1 with CG0070: control regimens
  - 6 week induction course
  - 3 and 9 month assessments
  - 15 month response as complete response
- Bond II
  - Open label HR NMIBC with Maintenance







Heat Biologics Intradermal Vaccine HS-410

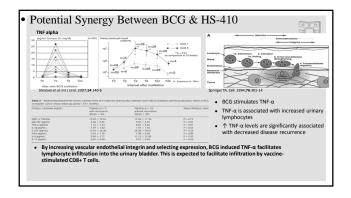
HS-410: an engineered "bladder tumor" cell line with added gp96 heat shock protein

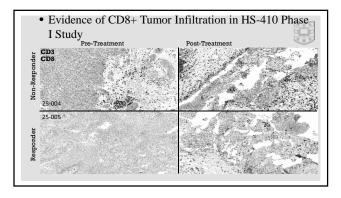
Produces bladder tumor antigens

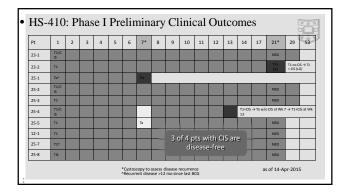
Produces an extracellular gp96 to continually deliver tumor antigens to CD8+ cells

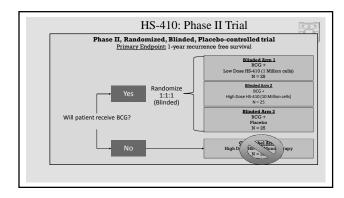
Administered intradermal, aim to be in combination with BCG

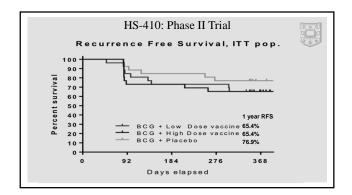
Goal is for superior CD8+ activation relative to BCG alone





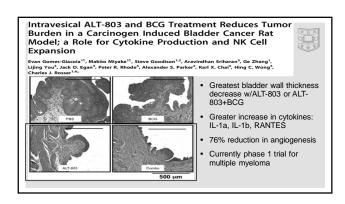


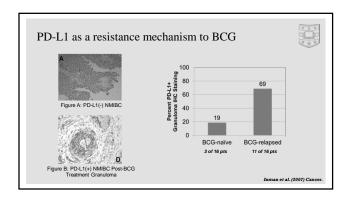




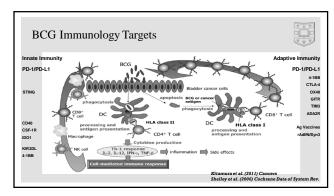
Intravesical ALT-803 and BCG Treatment Reduces Tumor Burden in a Carcinogen Induced Bladder Cancer Rat Model; a Role for Cytokine Production and NK Cell Expansion

E









#### Neoantigen vaccines



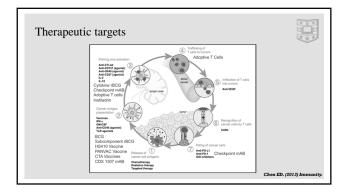
- Personalized neoantigen vaccines (NAV) induce broad immune responses, suggesting potential for synergy with an immune checkpoint inhibitor.<sup>1</sup>
- Two clinical trials are currently underway evaluating combination therapy with NAV + immune checkpoint inhibitor in UC.
  - NEO-PV-01 + nivolumab (NCT02897765)
  - PGV001 + atezolizumab (NCT03359239)
- Currently aimed at metastatic disease, but goal is to harness immune system to treat cancer in primary as well.

1. Ott et al. (2017) Nature

#### Immune checkpoints



- Normally immune checkpoints allow for self-tolerance
- Tumor cells exploit this regulatory pathway by over-expression of immune checkpoint molecules
- Therefore, novel therapies utilize monoclonal antibodies to block either the:
  - Immune checkpoint receptor (CTLA-4 or PD-1)
  - Immune checkpoint ligand (B7 or PD-L1)

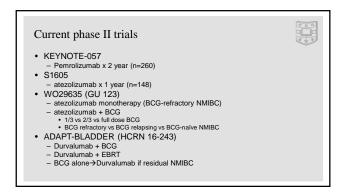


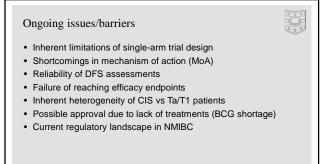
#### Timing of checkpoint inhibition

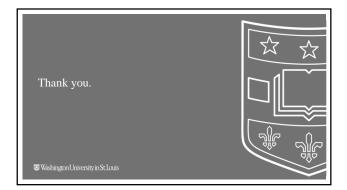


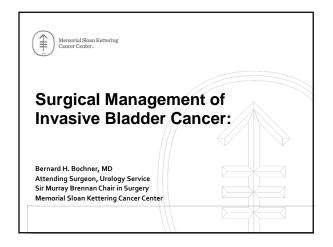
- Given highly successful utilization in metastatic setting, can timing be altered?
- BCG unresponsive disease?
- Neoadjuvant for MIBC?
- Adjuvant for high-risk MIBC?

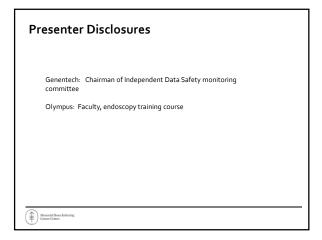
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## Radical Cystectomy For Bladder Cancer: GOALS

- · Local-regional control is the primary goal
- Surgical technique is critical
  - Key components: wide excision and PLND
- Surgical quality matters
  - Poor surgery leads to poor outcomes



## Simple Cystectomy: Lateral Dissection First performed 1888 (Bardenheuer) Simple cystectomy Adherent/adjacent fat only No regional lymph node dissection Stage procedure Fureteroenterostomy

> cystectomy

#### Cystectomy and Ureteroenterostomy: Operative Mortality and Survival

Author	Year	# patients	Mortality	Tumor recurrences
Hinman	1939	25	40%	53%
Priestley and Strom	1943	71	35%	31%
Jewett	1944	39	33%	50%
Smith	1947	47	21%	40%
Marshall	1947	81	16%	23%
Edelman	1947	34	29%	50%
Ferris and Priestley	1948	119	13%	37%

Memoral Stanz Kettring
Cancer Center.

Adapted from: Leadbetter and Cooper, J. Urol., 1950

#### Radical Cystectomy For Bladder Cancer: Lessons From Past

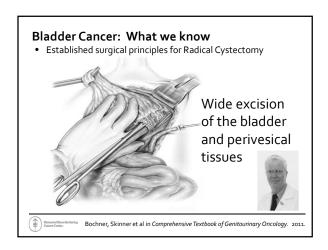
- 100 consecutive cystectomy patients
  - Little emphasis toward perivesical tissues and no regional LN dissection
- 26% "successful" 2 year outcomes
- 38 patients with persistent pelvic disease

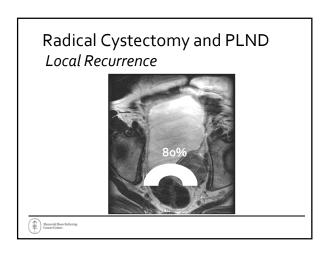
"The implications seems unavoidable that a more radical procedure might be worthy of trial..."



Marshall and Whitmore, J. Urol., 1950



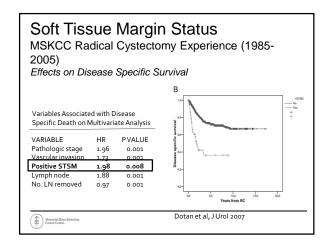


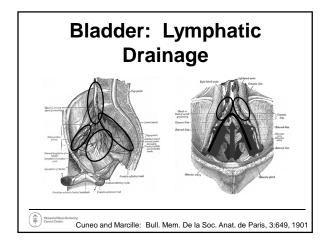


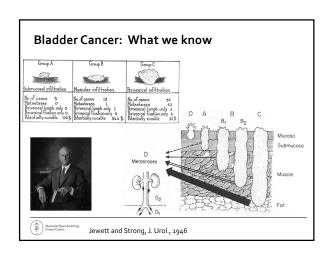
#### Radical Cystectomy and PLND Local Recurrence

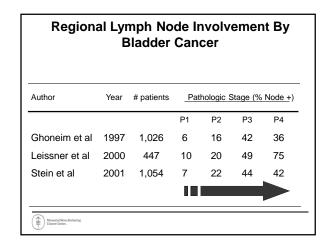
- Associated with stage of primary tumor
  - 6% OC; 13% NOC; (9% overall) (Stein et al JCO, 2001)
- Associated with soft tissue surgical margin status
  - 6% vs 21% (Dotan et al, J Urol 2007)
- Symptoms: pain (pelvic, perineal, lower extremity); bleeding; lower extremity or penile edema; bowel obstruction; constipation or priapism
- median time to a local recurrence 8-18 months
- median survival ranges from 4-8 months

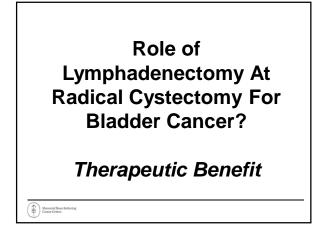
Memorial Sloan Kettering Cancer Center.

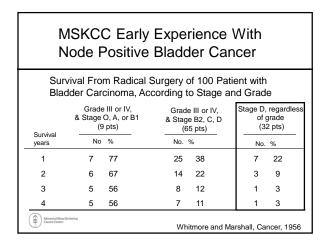


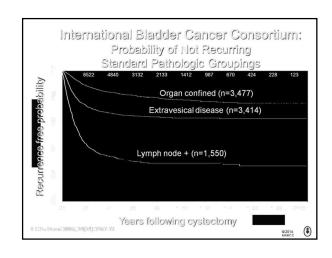


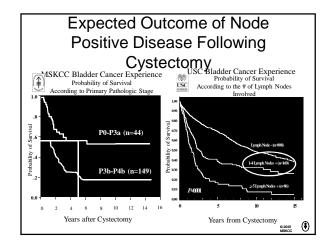






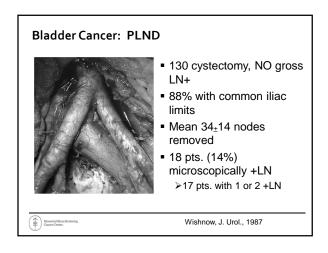


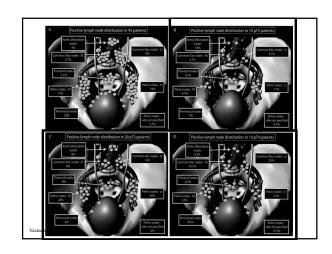


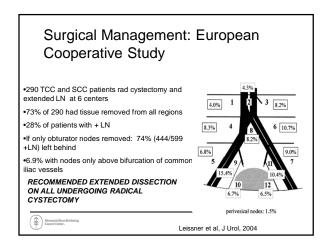


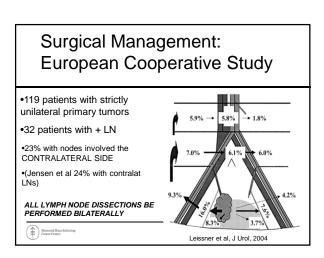
Role of
Lymphadenectomy in
Bladder Cancer

Extent of Dissection?









## **Surgical Quality For Invasive Bladder Cancer**

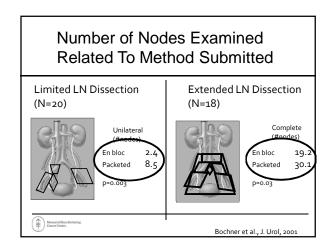
Is There A Recognized
Standard For The
Number Of Nodes That
Should Be Resected?

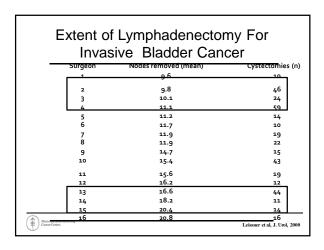


#### MSKCC Prospective LN Study Surgeon 3 (n=33 pts) 83% 66.7% 15.2% 61.5% 61.1% 25 (4-43) 24 (4-46) 17 (3-21) 22.5 (3-46) 18.4% 26.9% 60% 0 21.6% 2 (1-11) 3 (1-14) 1 (1-2) 0 2 (1-14) 17% 33.3% 84.8% 38.5% 38.9% 12 (4-27) 6 (0-25) 14 (4-36) 8 (0-36) 16 (7-24) 30.8% 14.3% 2.5 (1-3) 2.5 (2-3) 1.5 (1-2) 2 (1-3)

Bochner et al. J. Urol, 200

Extent of Lymphadenectomy

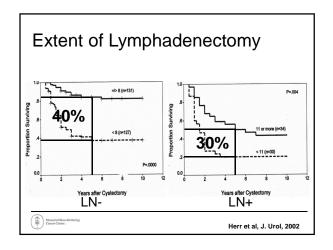


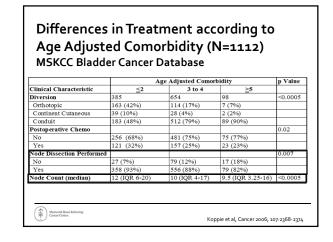


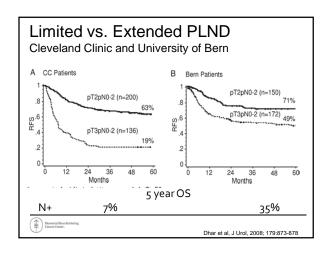
P value	Effect 95% CI
0.137	*
0.216	*
0.912	-4.4 to 4.9
0.082	-7.2 to 0.4
0.155	02 to 0.0
0.557	02 to 0.0
< 0.001	3.7 to 10.7
	0.137 0.216 0.912 0.082 0.155 0.557

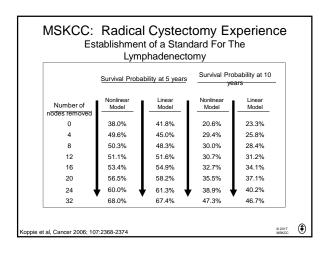
Therapeutic Role of Lymphadenectomy in Bladder Cancer

IS MORE BETTER??





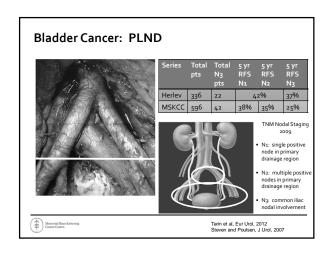


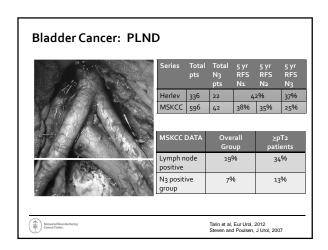


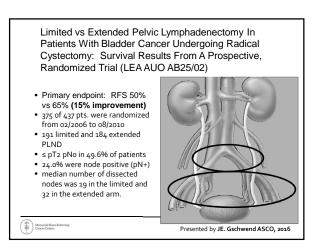
## **Surgical Quality For Invasive Bladder Cancer**

Outcome based on level of node positivity

Memorial Sloan Kettering Cancer Center.



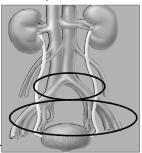




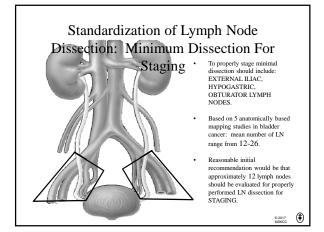
Limited vs Extended Pelvic Lymphadenectomy In Patients With Bladder Cancer Undergoing Radical Cystectomy: Survival Results From A Prospective, Randomized Trial (LEA AUO AB25/02)

- 5-year RFS: 62.0% in the limited compared to 69.3% in the extended arm (7.3% difference)
- Hazard ratio (HR) = 0.80, 95%
   (CI) (0.54-1.19); log-rank p = 0.28
- 5-year CSS: 66.2% in the limited;
   77.5% in the extended arm
- statistically not significant (HR = 0.70, 95%Cl 0.45-1.10; log-rank p = 0.13





Presented by JE. Gschwend ASCO, 2016



## TREATMENT OF NON-METASTATIC MUSCLE-INVASIVE BLADDER CANCER: AUA/ASCO/ASTRO/SUO GUIDELINE

Sam S. Chang, MD, MBA, FACS; Bernard H. Bochner, MD, FACS; Roger Chou, MD; Robert Dreicer, MD, MS, MACP, FASCO; Ashish M. Kamat, MD, MBBS, FACS; Seth P. Lerner, MD, FACS; Yair Lotan, MD; Joshua J. Meeks, MD, PhD; Jeff M. Michalski, MD, MBA; Todd M. Morgan, MD; Diane Z. Quale; Jonathan E. Rosenberg, MD; Anthony L. Zietman, MD; Jeffrey M. Holzbeierlein, MD, FACS



Chang et al, J Urol, 2017

#### TREATMENT OF NON-METASTATIC MUSCLE-INVASIVE BLADDER CANCER: AUA/ASCO/ASTRO/SUO GUIDELINE

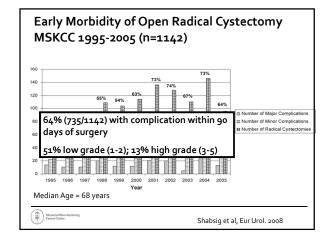
#### TREATMENT

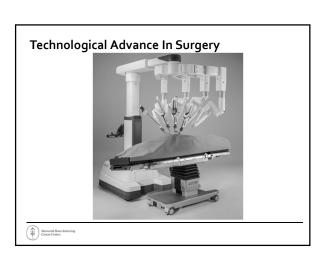
RADICAL CYSTECTOMY

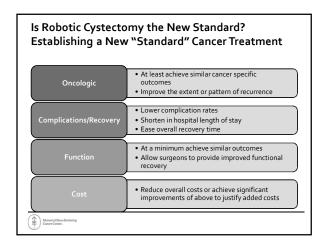
- Clinicians should offer radical cystectomy with bilateral pelvic lymphadenectomy for surgically eligible patients with resectable non-metastatic (Mo) muscle-invasive bladder cancer. (Strong Recommendation; Evidence Level: Grade B).
- When performing a standard radical cystectomy, clinicians should remove the bladder, prostate, and seminal vesicles in males and should remove the bladder, uterus, fallopian tubes, ovaries, and anterior vacinal wall in females. (Clinical Principle)
- Clinicians should discuss and consider sexual function preserving procedures for patients with organ-confined disease and absence of bladder neck, urethra, and prostate (male) involvement. (Moderate Recommendation; Evidence Level: Grade C)

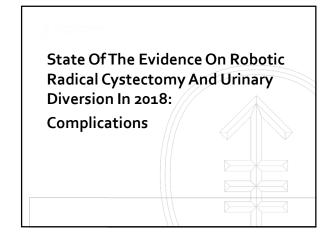
Memorial Stoan Ketteric Cancer Center.

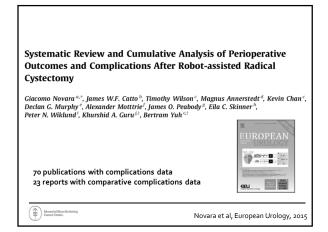
Chang et al, J Urol, 2017

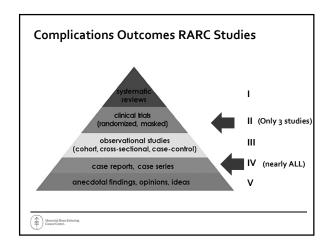


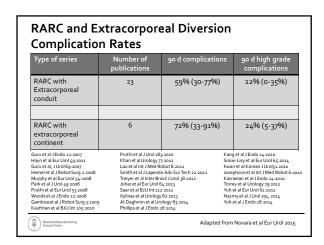








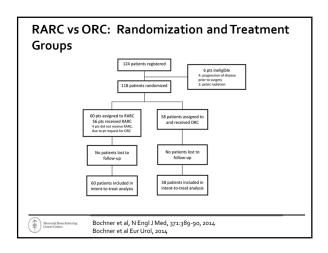




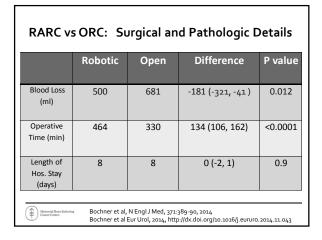


### MSKCC RARC vs ORC: Methodology Expertise Trial Design: high volume surgeons with extensive robotic and open experience included All RARC patients operated by experienced robotic surgeons, all open patients operated by open surgeons (open surgeons completing all diversions open) All patients managed on identical standardized post operative pathway (4-5d discharge possible)

Bochner et al, N Engl J Med, 371:389-90, 2014 Bochner et al Eur Urol, 2014, http://dx.doi.org/10.1016/j.eururo.2014.11.043



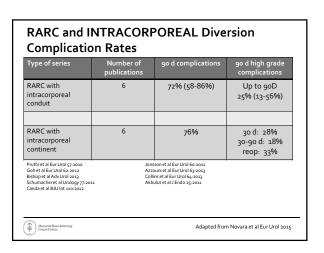
### Primary Outcome: 90 day Complications Outcome Difference p-value (N=6o) (95% CI) % Patients 62% 66% -3.9% Grade 2-5 0.7 (-21%, 13%) % Patients 22% 21% 1.0% Grade 3-5 0.9 (-14%, 16%) Length of Hos. 8 0 (-2, 1) 0.9 Stay (days) Bochner et al, N Engl J Med, 371:389-90, 2014 Bochner et al Eur Urol, 2014, http://dx.doi.org/10.1016/j.eururo.2014.11.043

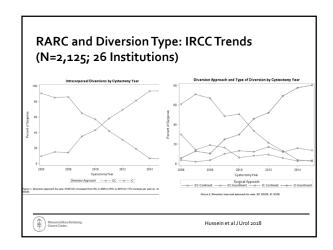


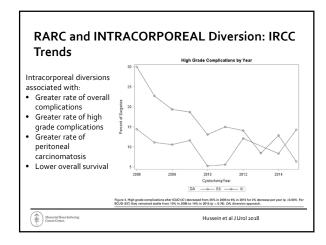
### Comparing RARC and ORC Conclusions RARC appears comparable to ORC in terms of safety with similar complication rates RARC leads to lower blood loss and transfusion requirements at the cost of longer OR times RARC and ORC can provide similar pathologic outcomes including margin rates and LN yields There does not appear to be an advantage of RARC over ORC

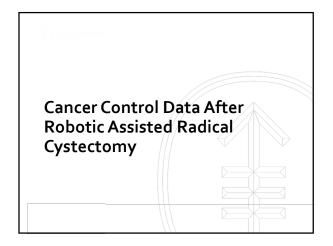
Bochner et al, N Engl J Med, 371:389-90, 2014 Bochner et al Eur Urol, 2014, http://dx.doi.org/10.1016/j.eururo.2014.11.043

**MSKCC Prospective, Randomized Trial** 









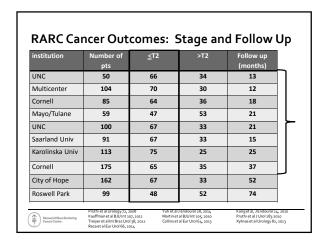
Systematic Review and Cumulative Analysis of Oncologic and Functional Outcomes After Robot-assisted Radical Cystectomy

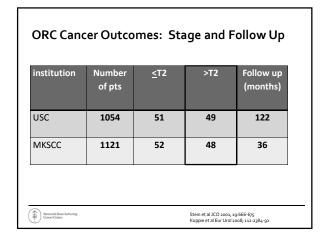
Bertram Yuh "\*, Timothy Wilson ", Bernie Bochner ", Kevin Chan ", Joan Palou ", Arnulf Stenzi ", Francesco Montorsi", George Thalmann ", Khurshid Guru ", James W.F. Catto ", Peter N. Wiklund ", Giacomo Novara ".

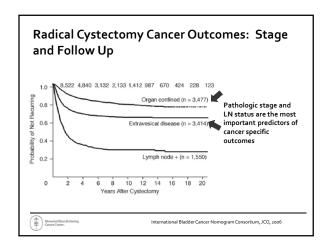
RARC Pasadena Consensus Panel – Review

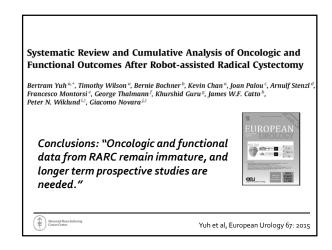
Only 18 publications reporting survival data
All survival data Level 4 evidence

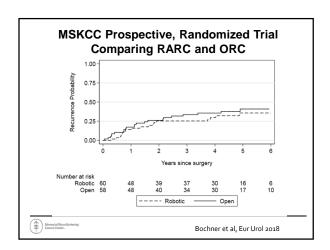
Yuh et al, European Urology 67: 2015

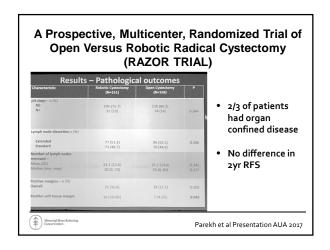


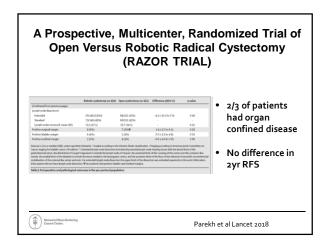


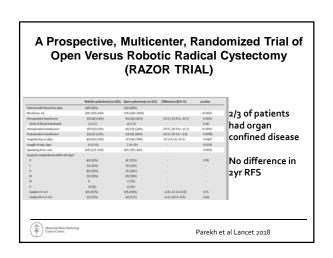


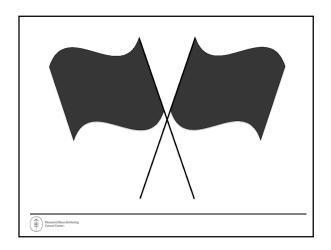


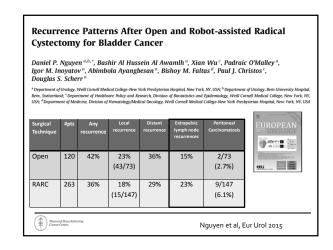


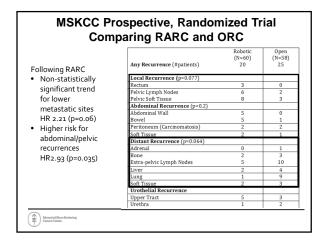


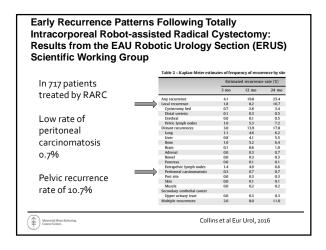


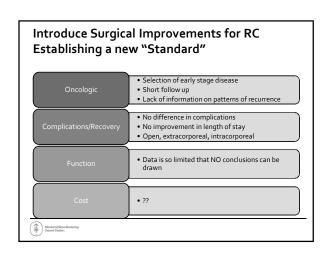


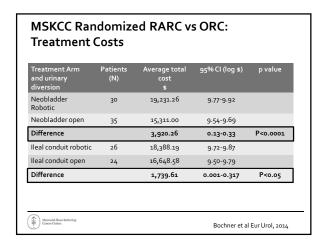










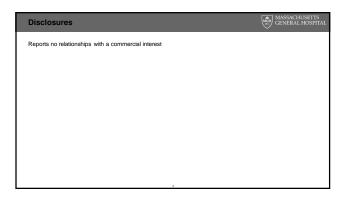


Have we established a new standard for the surgical treatment bladder cancer?

Have we established a new standard option for the surgical treatment bladder cancer?

Yes, but...





### Session Learning Objectives



- Review prospective randomized trials and large institutional experiences utilizing tri-modality therapy for muscularis propria invasive bladder cancer
- · Discuss which patients are candidates for tri-modal bladder sparing therapy, and which patients are not candidates and should instead undergo radical cystectomy
- · Describe the technique and importance of aggressive initial transurethral resection, repeat transurethral resection and ongoing cystoscopic surveillance of the bladder
- Describe the coordinated multidisciplinary technique in tri-modality therapy, including radiosensitizing chemotherapy agents, radiation, and adjuvant chemotherapy
- Describe the indications for salvage cystectomy, discuss management of noninvasive recurrences, and understand the quality of life and potential toxicities after tri-modal therapy

- 1. Rationale for bladder sparing tri-modal therapy
- 2. Patient selection for TMT vs. radical cystectomy
- 3. Importance of coordinated multi-disciplinary care
- 4. Critical role of aggressive TURBT and repeat TURBT
- 5. TMT paradigm and outcomes
- 6. Chemotherapy options and delivery with TMT
- 7. Surveillance, follow-up and addressing recurrences after TMT: NMIBC and MIBC
- 8. Quality of life, predictive biomarkers and future advances

### Rationale for bladder sparing tri-modal therapy

Organ conservation by tri-modality therapy (TMT) is commonplace in contemporary oncology

- Laryngeal carcinoma
- Anal carcinoma Breast carcinoma
- Esophageal carcinoma
- Limb sarcomas

In primary muscle-invasive bladder cancer (MIBC), radical cystectomy remains the most commonly offered treatment

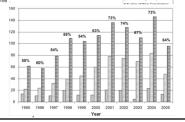
There are no completed randomized trials comparing bladder-preserving TMT

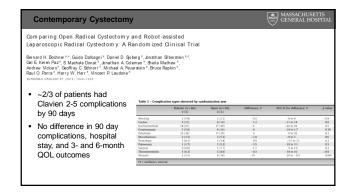
While most patients do well, it is a major physiologically challenging surgery and can be life altering

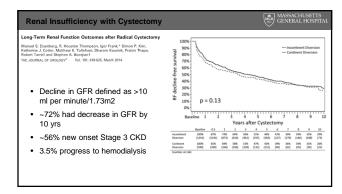
### Defining Early Morbidity of Radical Cystectomy for Patients with Bladder Cancer Using a Standardized Reporting Methodology • 64% of patients experienced a complication within 90 days

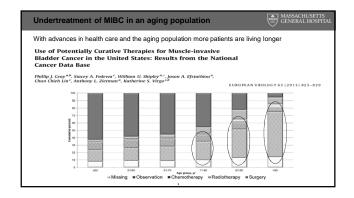
Complications of radical cystectomy

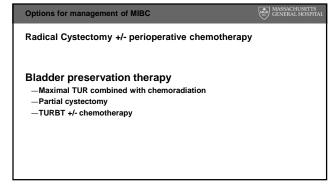
- 13% had high-grade (Clavien 3-5) complication
- · 26% readmission rate
- 2.7% 90 day mortality

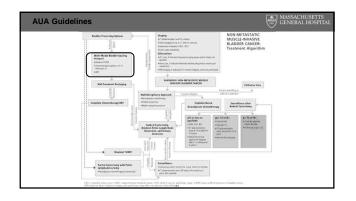


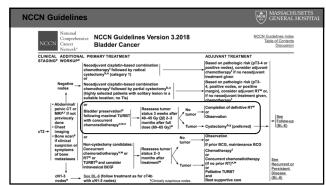


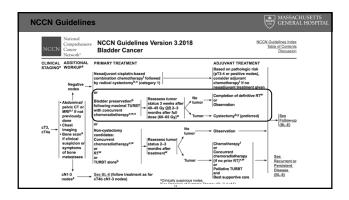


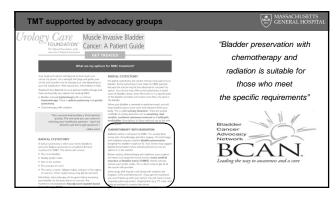


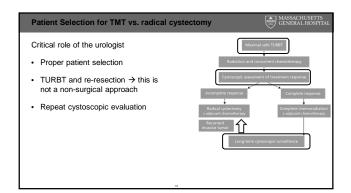


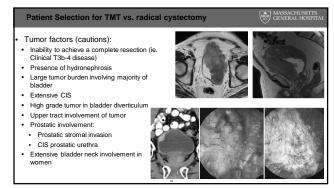


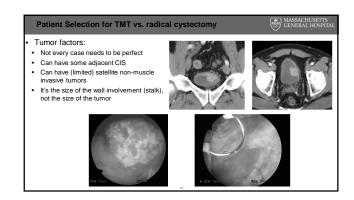


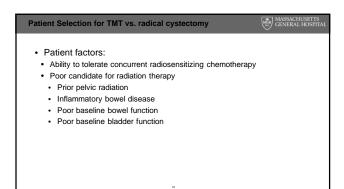


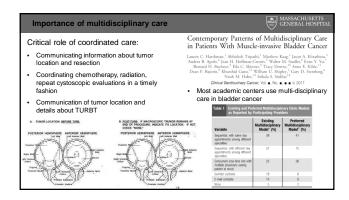


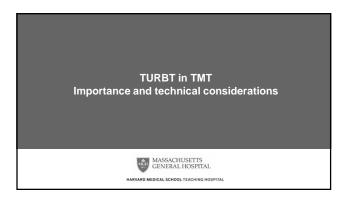


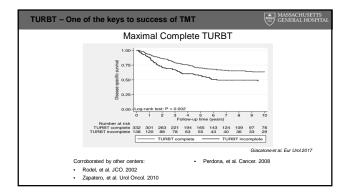


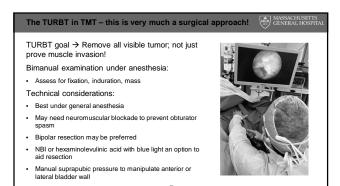


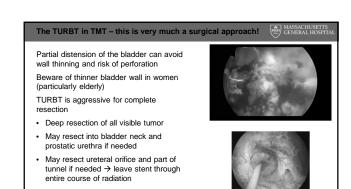


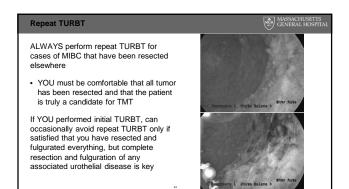


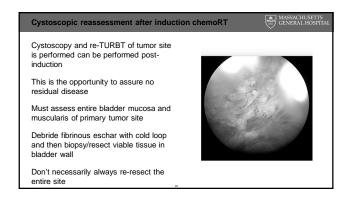


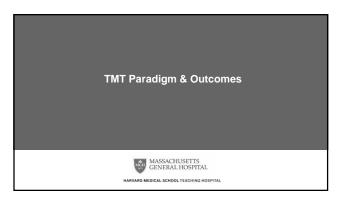


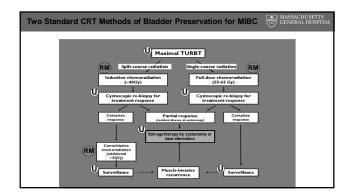


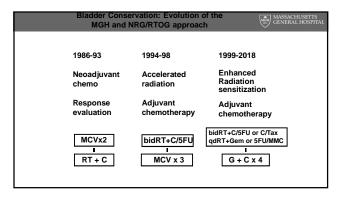


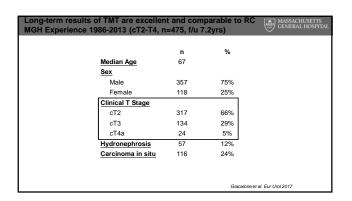


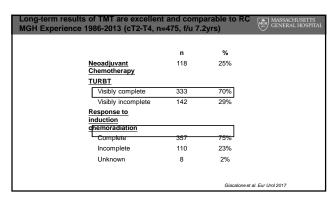


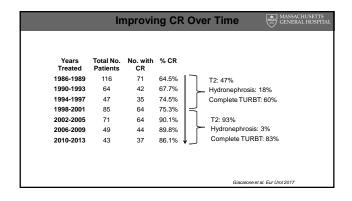


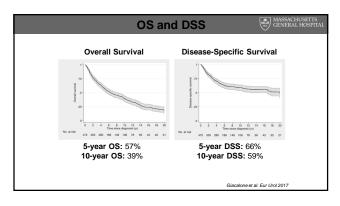


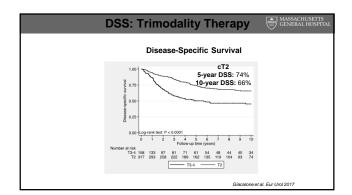


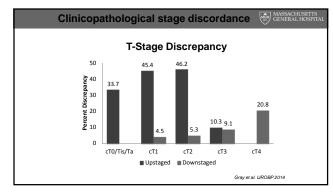


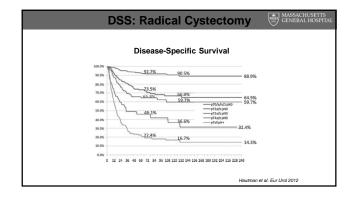


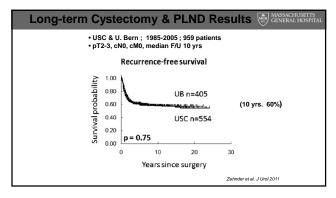




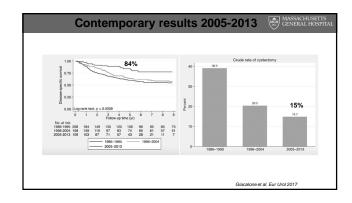


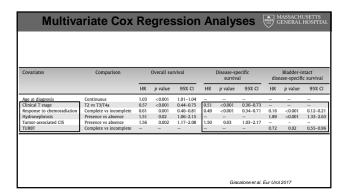


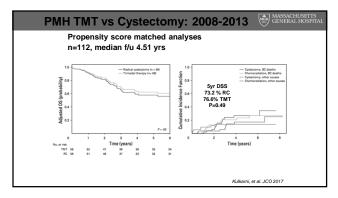


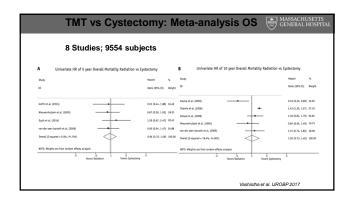


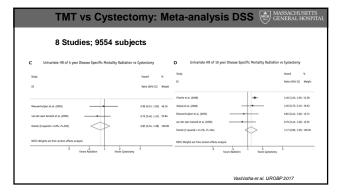
Survival after curative therapy GENERAL HOSPIT							
I		Stage	Number	5 year OS	10 year OS		
	Cystectomy USC 2001	pT2-4a	633	48%	32%		
	MSKCC 2001	pT2-4a	181	36%	27%		
	SWOG 2003	cT2-3	303	49%			
	Chemo-RT RTOG 1998	cT2-4a	123	49%	-		
	Erlangen 2002	cT2-4	326	45%	29%		
	MGH 2017	cT2-4a	348	57%	39%		
	BC2001 2012	cT2-4a	182	48%	-		
	RTOG pooled 2014	cT2-4a	468	57%	36%		

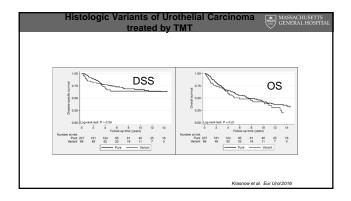


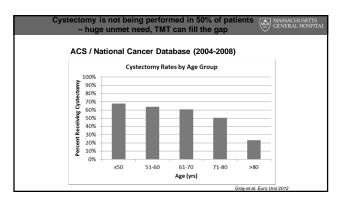


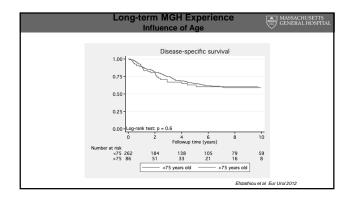


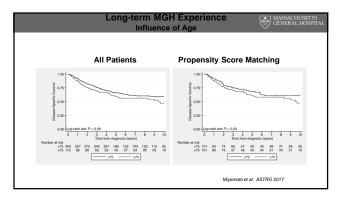


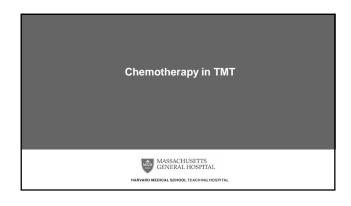


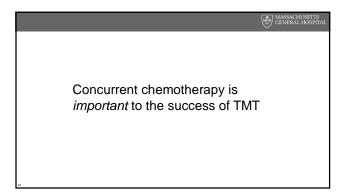


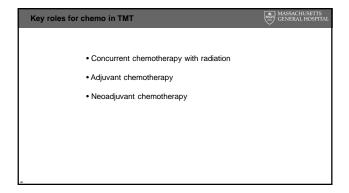


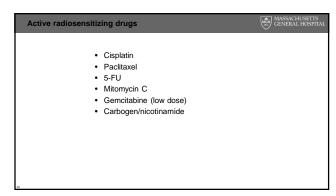


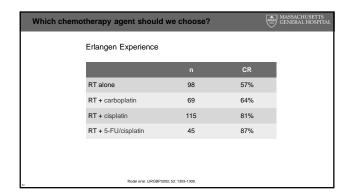


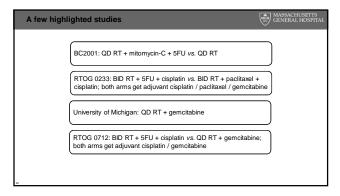


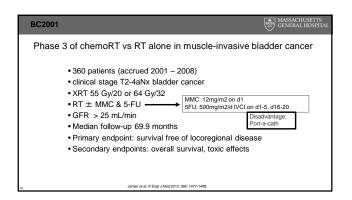


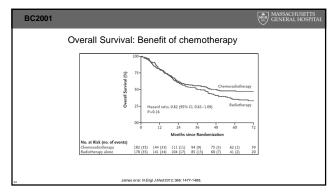


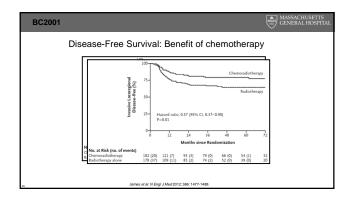


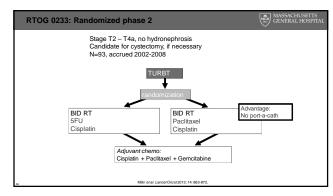


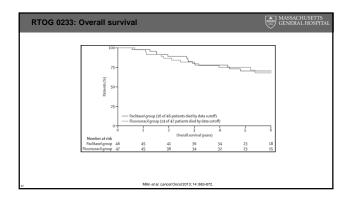


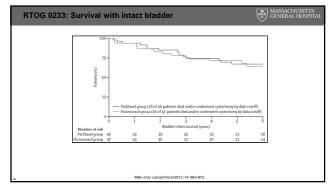


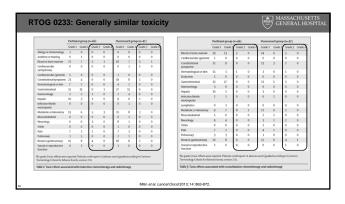


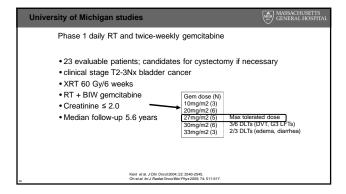


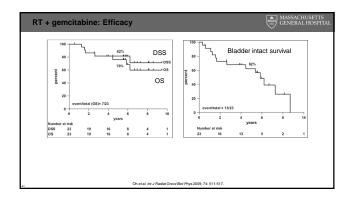


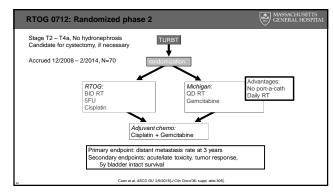


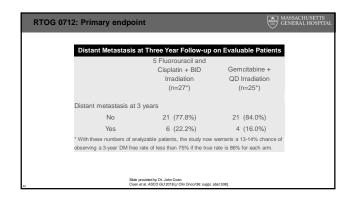


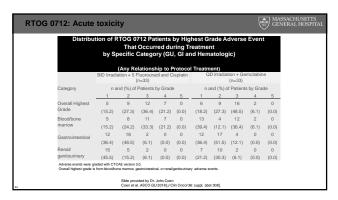


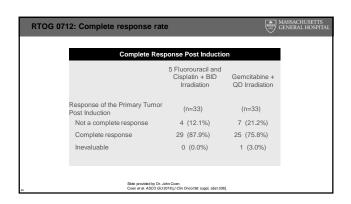


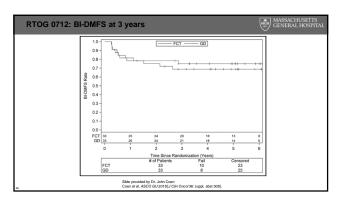


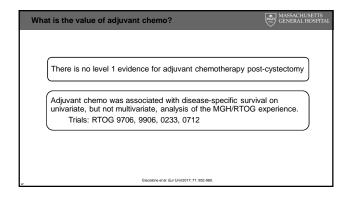


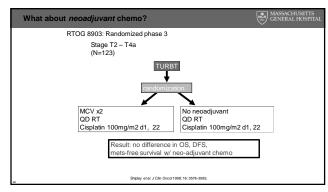


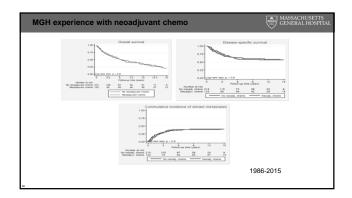


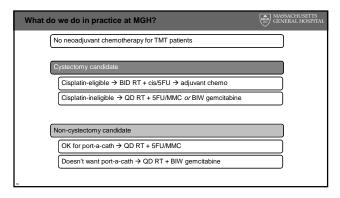




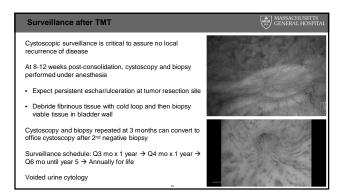


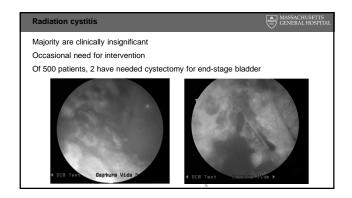


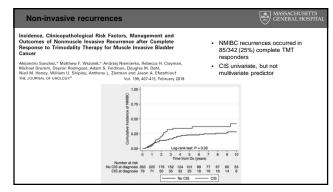


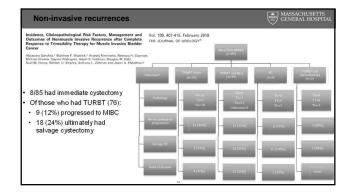


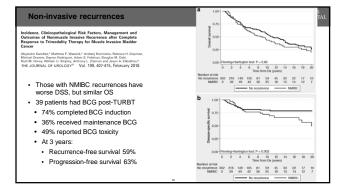


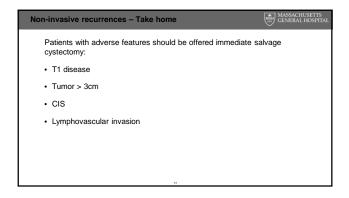


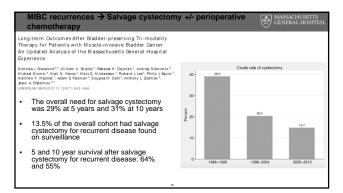


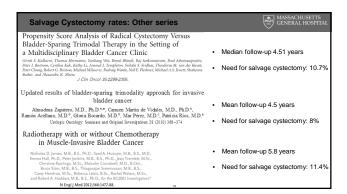


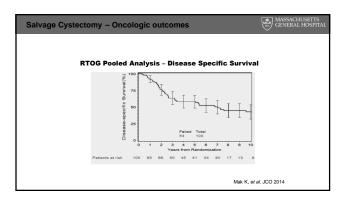


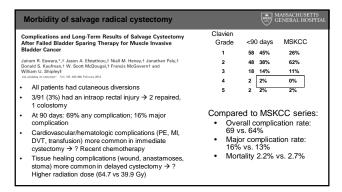


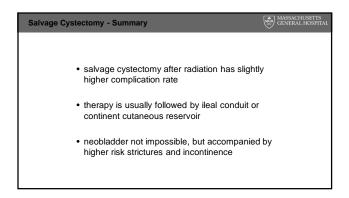




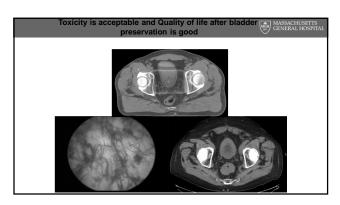












### **TMT Clinical Trials**

MASSACHUSETTS GENERAL HOSPITA

 RTOG trials: 157 patients treated with TMT who survived 2-13 years (median follow-up 5.2 years)

Late Pelvic Toxicity				
Grade 1	22%			
Grade 2	10%			
Grade 3	7.6% (5.7% GU, 1.9% GI)			
Grade 4	0%			
Grade 5	0%			

BC2001: 360 patients treated with radiation vs. TMT
 Grade 3-4 late toxicity: GU 3.3%; GI 0.8%

Efstathiou JA, et al. JCO 2009 James ND, et al. NEJM 2012

### MGH Urodynamics and QOL Study

MASSACHUSETTS

221 patients treated with TMT on protocols 1986-2000, median follow-up 6.3 years

- 78% have compliant bladders with normal capacity and flow parameters
  - · 85% have no or occasional urgency
- 25% have occasional to moderate bowel control symptoms
- · 50% of men have normal erectile function

Zietman AL, et al. J Urol 2003

### 

Comparing Quality of Life after Surgery vs. Trimodality Therapy AASSACHUSETIS GENERAL HOSPITAL

Little data comparing quality of life (QOL) after radical cystectomy (RC) vs. TMT<sup>1</sup>

- Randomized trial comparing RC to TMT (SPARE) closed early due to poor accrual<sup>2</sup>
- Both treatments have long-term effects on overall QOL, urinary, bowel, and sexual function, and selfimage<sup>3</sup>

Lagrange JL, et al. IJROBP 2011
 Huddart RA, et al. BJU Int 2010
 Porter MP, et al. J Urol 2005

### Cystectomy vs. Radiation



Cross-sectional study from Karolinska Institute, Sweden 251 patients treated with cystectomy (incontinent and continent diversions) 58 patients treated with radiation 310 "control" individuals from general population

Urinary function

After radiation: 74% had no or little urinary symptom distress

Rowel function

- After radiation: 32% had moderate or much bowel distress
- After cystectomy: 24%
   Control group: 9%

Sexual function

- After radiation: 38% had intercourse in last month
- After cystectomy: 13%

Henningsohn L, et al. Radiother Oncol 2002

### Review of TMT QOL Studies

MASSACHUSETTS

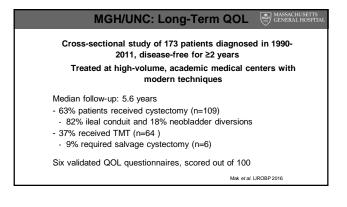
Systematic review of 6 QOL studies after TMT (2 prospective, 4 retrospective)

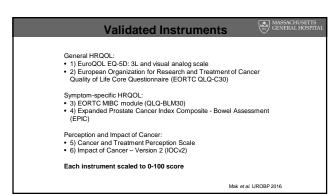
TMT associated with:

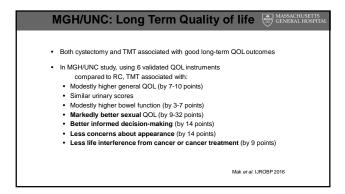
- Good general QOL compared to cystectomy
- Satisfactory urinary function
- Likely more bowel symptoms than cystectomy
- Satisfactory sexual function

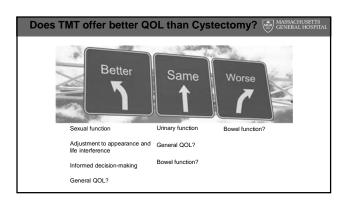
Included studies were limited by sample size, variable follow-up, and non-validated instruments

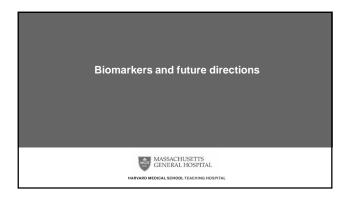
Feuerstein MA, et al. Curr Urol Rep 201

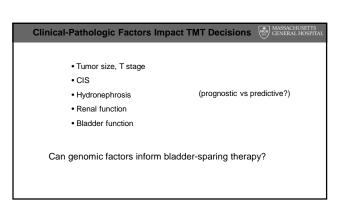


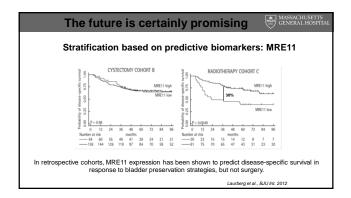


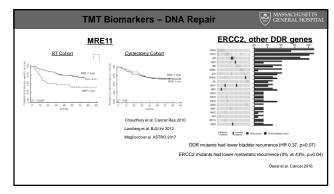


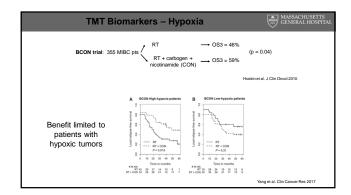


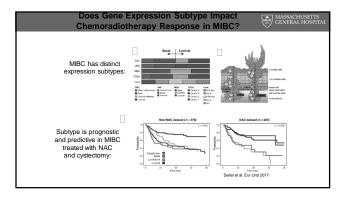


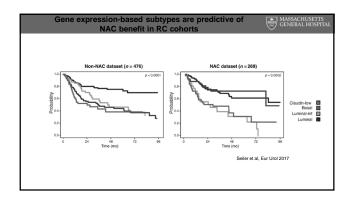


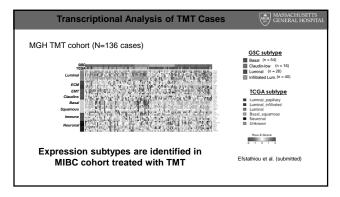


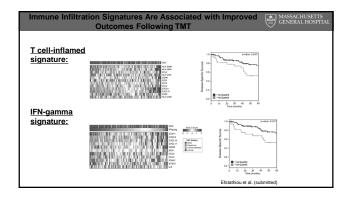


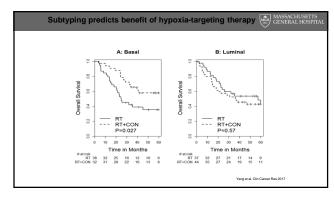


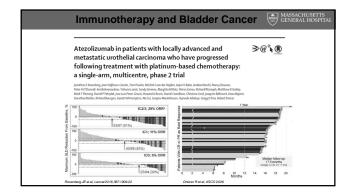


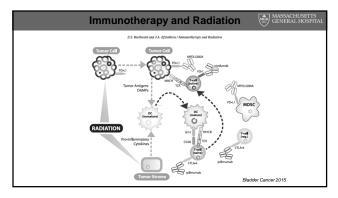


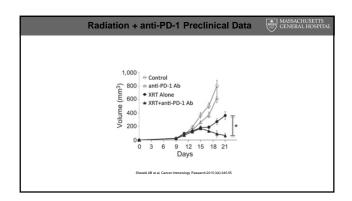


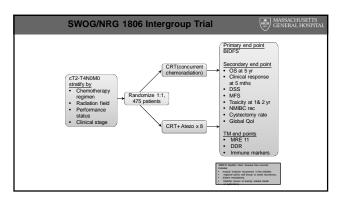


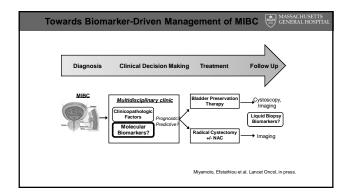


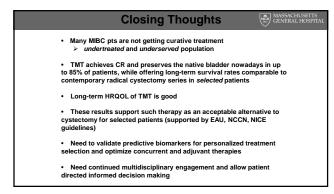


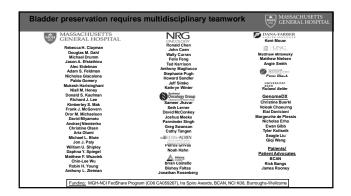


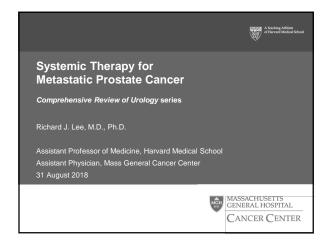


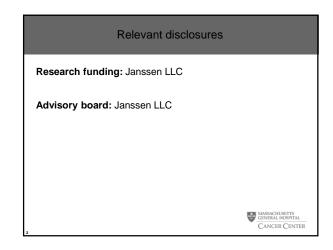








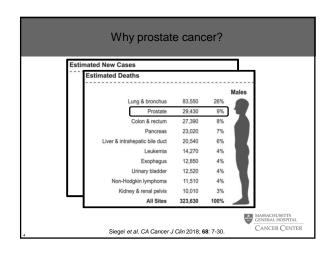


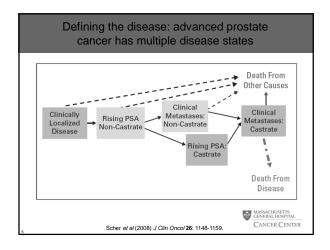


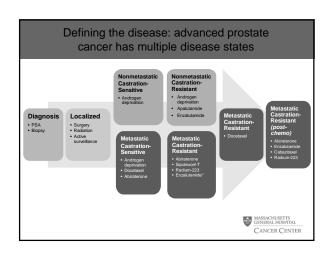
1. Discuss data regarding the use of systemic therapy in patients with recurrent/metastatic prostate cancer

2. Describe possible sequences of therapies for patients with metastatic prostate cancer

WASSACHUSETTS CANCER CENTER

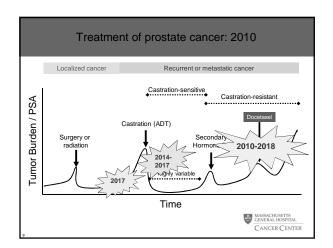


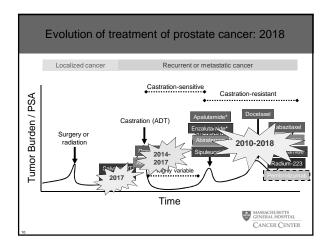


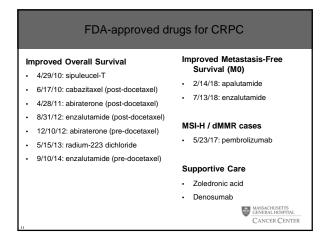


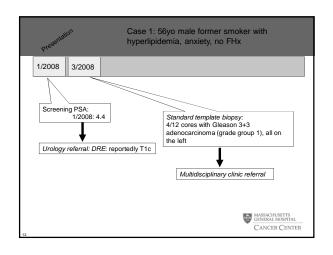
# Androgen deprivation therapy = castration therapy Goal: lower testosterone (T) to castrate levels Surgical castration (bilateral orchiectomy) Medical castration GnRH agonists (leuprolide, goserelin, triptorelin, buserelin, histrelin) GnRH antagonist (degarelix)

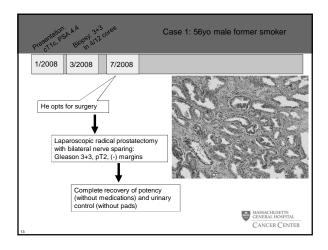
# Some more definitions Anti-androgens Mechanism: bind and block androgen receptor (AR) Examples: bicalutamide, flutamide, nilutamide, enzalutamide, apalutamide Steroidogenesis Inhibitors Mechanism: inhibit non-testicular production of T Examples: ketoconazole, abiraterone

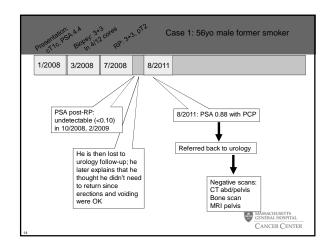


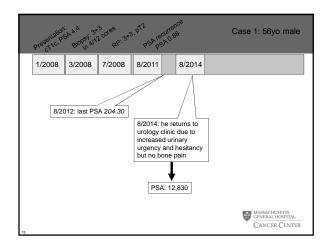


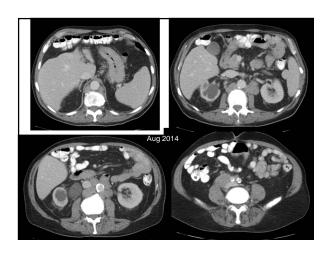


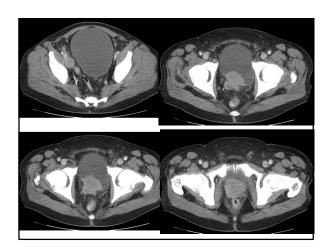




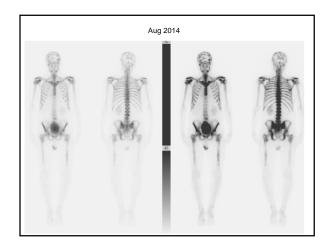


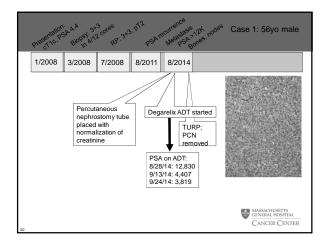


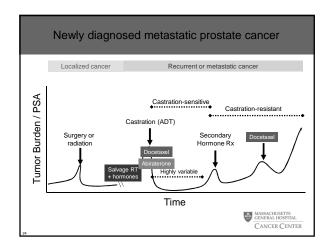


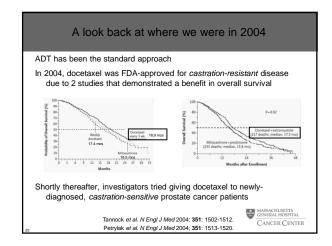












### What about earlier use of docetaxel in metastatic castration-sensitive prostate cancer?

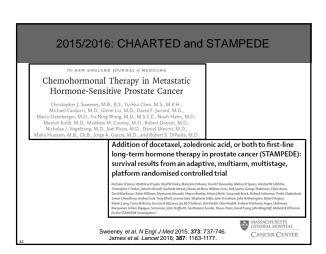
### Pros

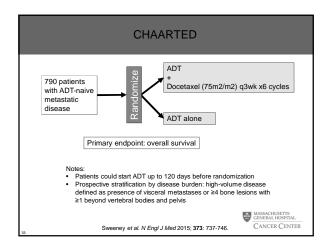
- · Attack testosterone-independent clones early
- · Might allow ADT to keep disease in remission for longer period of time
- Some patients at the time of progression are too frail for chemo

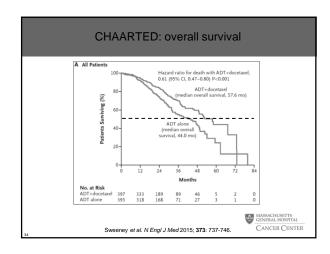
### Cons

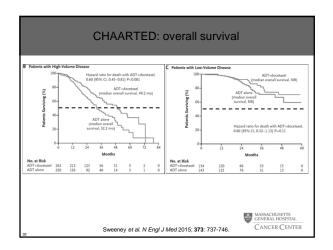
- ADT may take cells out of cycle, making them less responsive to cytotoxics
- Some patients response to ADT for a long time and never need chemotherapy (overtreatment)

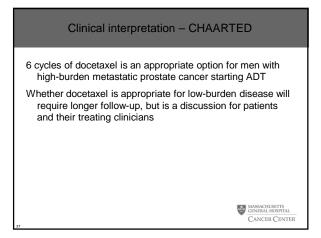


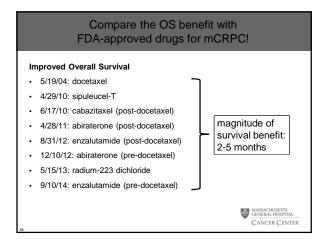


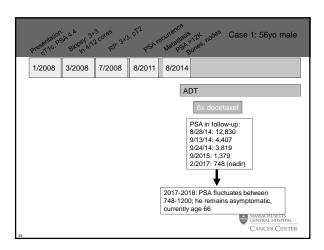






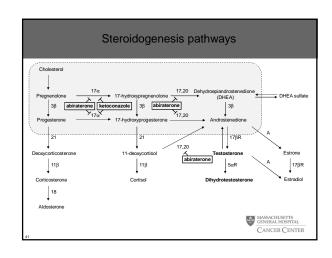


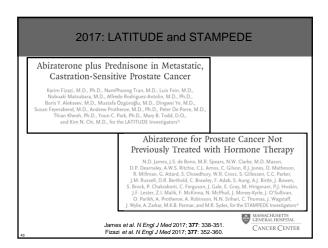


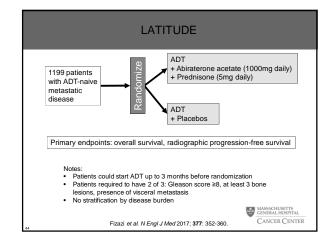


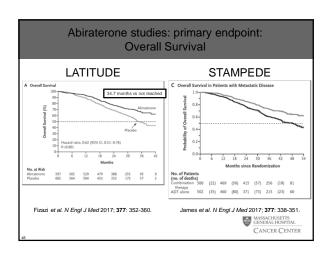
CANCER CENTER

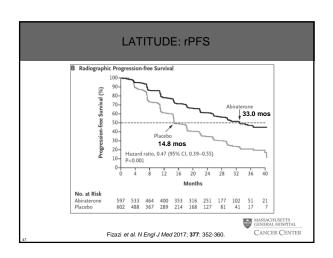
## What about earlier use of abiraterone in metastatic castration-naïve prostate cancer? Background Abiraterone inhibits cytochrome P450c17 and thus inhibits androgen biosynthesis, including extragonadal synthesis (adrenal, intratumoral) Abiraterone increased overall survival in the metastatic castration-resistant prostate cancer (mCRPC) setting Abiraterone has been shown to decrease tumor burden in high-risk localized disease as neoadjuvant therapy Abiraterone acetate is orally bioavailable Question Is there a benefit to inhibiting extragonadal androgens before the development of castration resistance?

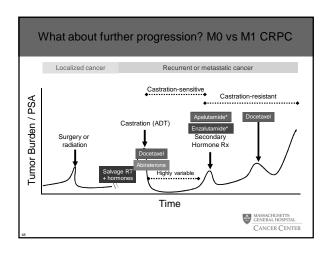


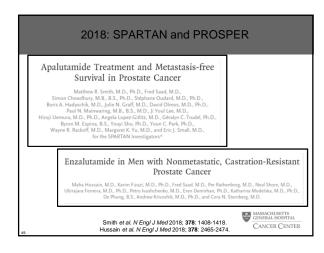


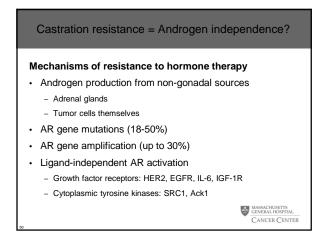


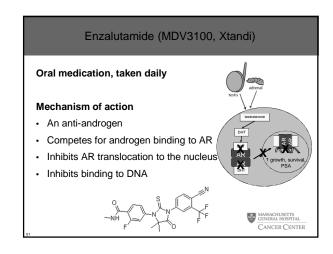


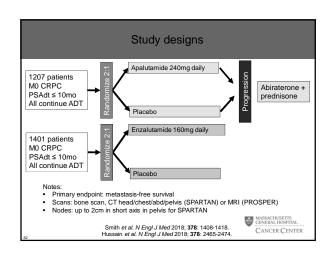


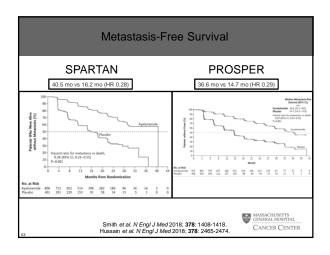


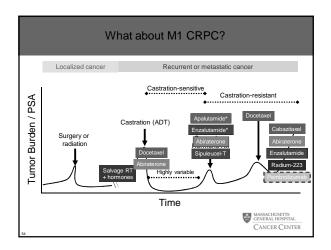


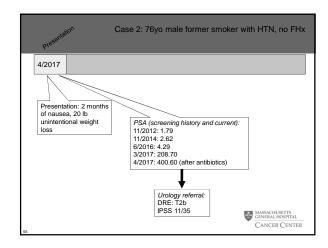


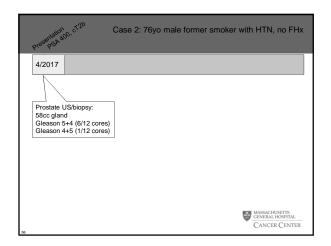


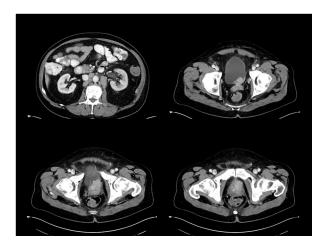


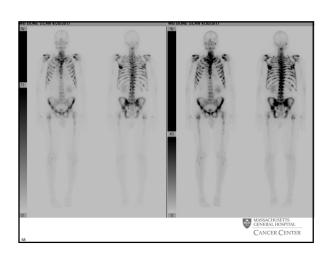


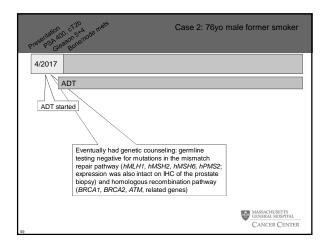


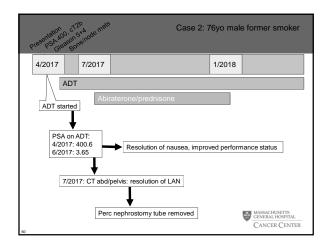


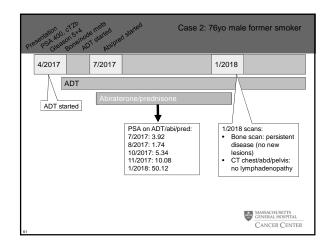


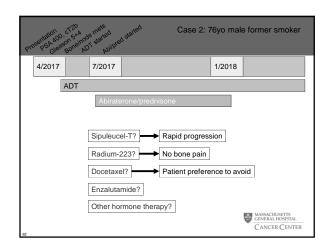


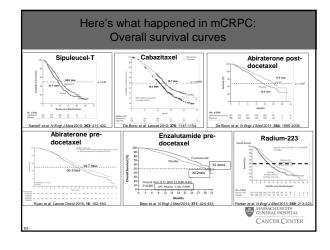


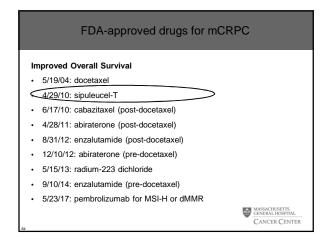


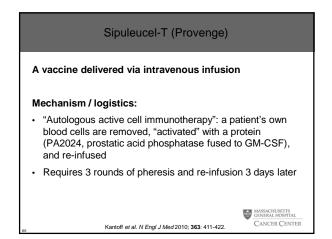


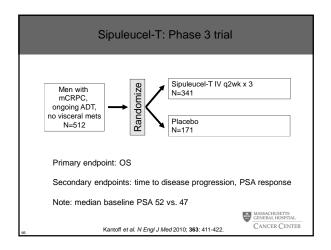


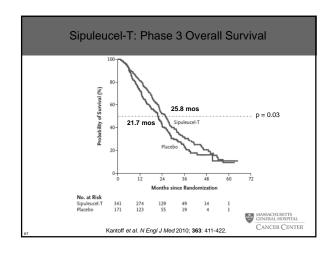




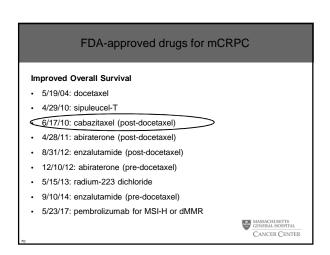


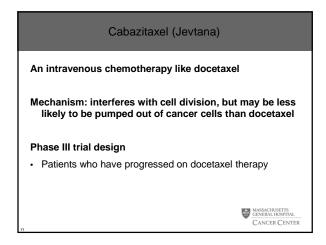


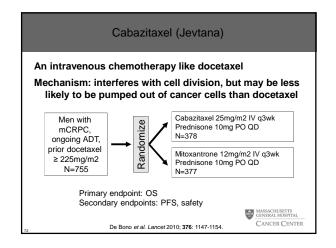


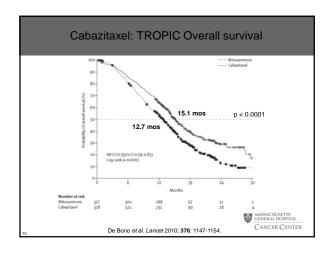


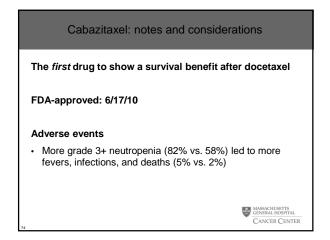
# Sipuleucel-T: considerations How do you know if it's working? PSA does not change Time to disease progression was not different FDA-approved: 4/29/10 How is sipuleucel-T optimally sequenced with other therapies that include immunosuppressants? Cost: is a 4 month improvement "worth it"? \$93,000 for all 3 infusions

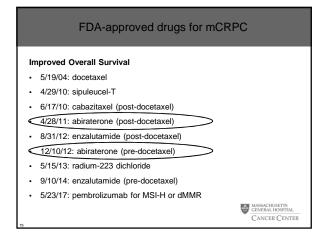


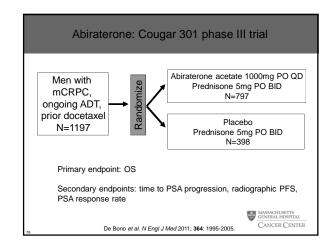


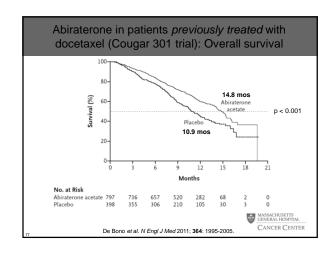




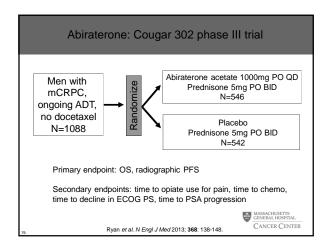


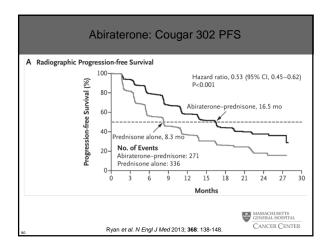


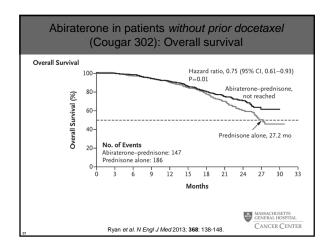


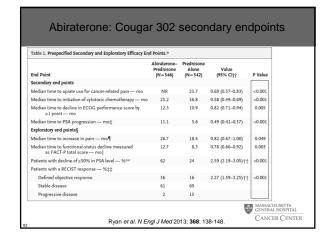


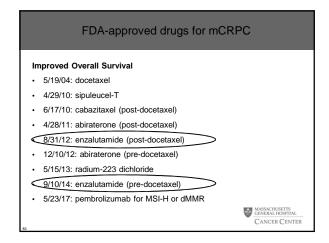
# Abiraterone: considerations The second drug (after cabazitaxel) to show a survival benefit after docetaxel Longer progression free survival: 5.6 mos vs. 3.6 mos. Might there be a benefit when given before docetaxel chemotherapy? The Cougar 302 study (Phase 3, randomized controlled trial in chemo-naïve patients)...

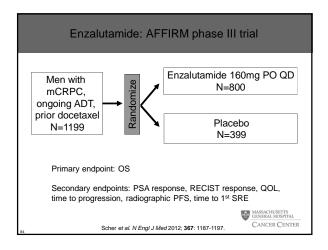


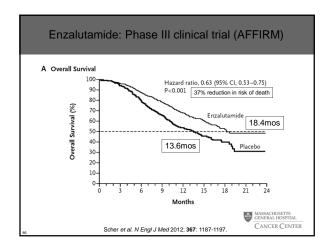


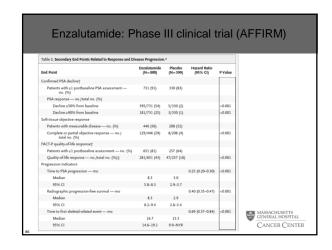


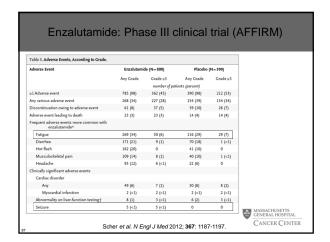


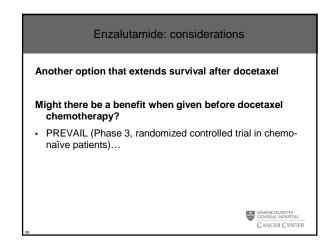


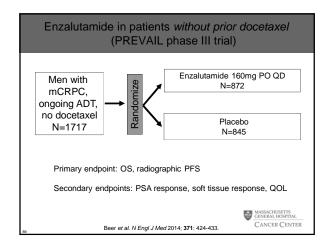


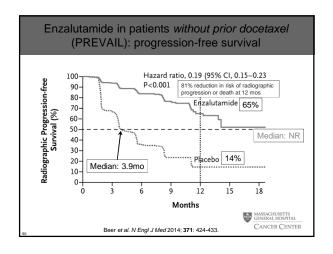


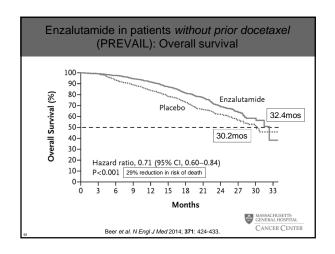


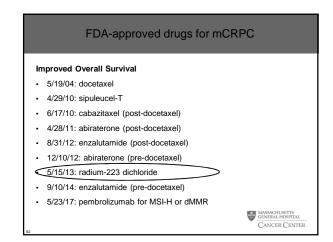




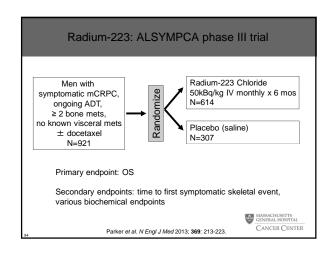


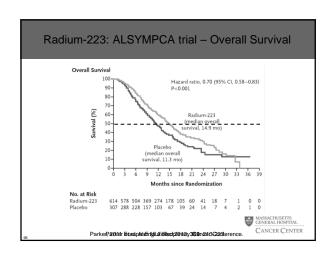


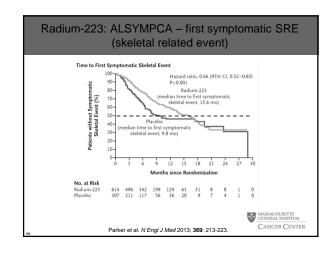




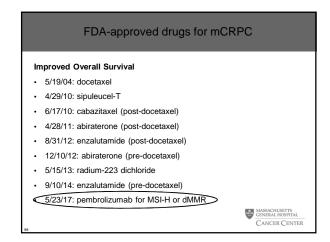
# An intravenous radiation treatment Mechanism • A radioisotope containing an α-emitting nuclide • Targets bone metastases with high-energy α radiation of extremely short range that spares bone marrow, limiting toxic effects • For patients with bone-only or bone-dominant disease Logistics: monthly infusions x 6 months

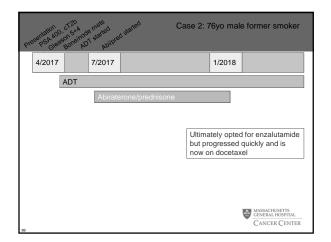


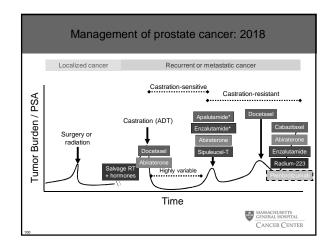




Agent(s)	N	OS	improvement	P
Mitoxantrone + hydrocortisone	119	12.3mo	0.0	0.77
Hydrocortisone	123	12.6mo	0.3mo	0.77
Docetaxel/estramustine	338	17.5mo	4.0	0.02
Mitoxantrone	336	15.6mo	1.9mo	0.02
Docetaxel/prednisone q3wk	335	18.9mo		0.009
Docetaxel/prednisone q1wk	334	17.4mo	2.4mo	
Mitoxantrone/prednisone q3wk	337	16.5mo		0.36
Abiraterone acetate/prednisone	546	34.7mo	4 4000	0.01
Placebo/prednisone	542	30.3mo	4.41110	0.01
Sipuleucel-T	341	25.8mo	4.4500	0.03
Placebo	171	21.7mo	4.11110	0.03
Radium-223 chloride	541	14.0mo	2 0	0.00046
Placebo	268	11.2mo	2.01110	0.00046
Cabazitaxel/prednisone	378	15.1mo	2.450	0.0004
Mitoxantrone/prednisone	377	12.7mo	2.4MO	<0.0001
Abiraterone acetate/prednisone	797	14.8mo	0.0	<0.001
Prednisone	398	10.9mo	3.9mo	<0.001
Enzalutamide	800	18.4mo	4.8mo	<0.001
	Mitosantrone + hydrocortisone Hydrocortisone Docetaxel/estramustine Mitosantrone Docetaxel/estramustine Mitosantrone Docetaxel/prednisone q3wk Docetaxel/prednisone q3wk Mitosantrone/prednisone q3wk Abiraterone acetate/prednisone Placebo/prednisone Placebo/prednisone Sipuleucel-T Placebo Radium-223 chloride Placebo Cabazitaxel/prednisone Mitosantrone/prednisone Mitosantrone/prednisone Mitosantrone/prednisone Prednisone	Mitoxantrone + hydrocortisone         119           Hydrocortisone         123           Docetazelé estramustine         336           Mitoxantrone         336           Mozetazelé prednisone q3wk         335           Docetazelé/prednisone q1wk         334           Mitoxantrone/prednisone         546           Placobo/prednisone         542           Spulaeucel**         341           Placobo/prednisone         171           Radium-223 chloride         541           Placebo         268           Cabazitaxel/prednisone         378           Mitoxantrone/prednisone         377           Abiraterone acetate/prednisone         398	Mitoanirone + hydrocortisone         119         12.3mo           Hydrocortisone         123         12.6mo           Docetaxel/estramustine         338         17.5mo           Mitoanirone         336         15.6mo           Docetaxel/prednisone q3wk         335         18.9mo           Docetaxel/prednisone q3wk         337         16.5mo           Abiraterone acetatel/prednisone         546         34.7mo           Placebol prednisone         542         30.3mo           Spipuleucel-T         341         25.8mo           Placebo         171         21.7mo           Radium-223 chloride         541         14.0mo           Placebol         268         11.2mo           Cabazitaxeli/prednisone         378         15.1mo           Mitoantrone/prednisone         377         12.7mo           Abiraterone acetate/prednisone         398         10.9mo	Millocaritrone + hydrocortisone   119   12.3mo   12.3mo   1.2 mo   0.3mo   0.







# Despite all the progress, there's work to be done

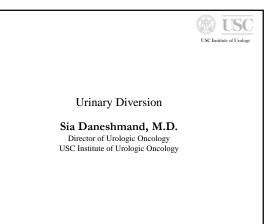
#### **Outstanding questions**

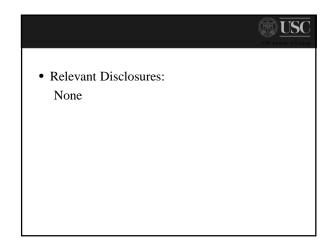
- · With so many drugs, what is the optimal sequence?
- · What do we know about resistance to therapies?
- Can we identify cellular changes (genetic or other) that may explain more aggressive cancer behavior in black patients?
- · What is the role for immunotherapy? Who benefits?

#### **Outstanding needs**

- Predictive biomarkers for aggressive disease, treatment response, intermediate endpoints
- · New imaging techniques







# Urinary Diversion at USC USC



- Orthotopic diversion is arguably the gold standard
- Every patient undergoing radical cystectomy is considered for an orthotopic diversion, except when one or more contraindications apply.

# **SEER Data**

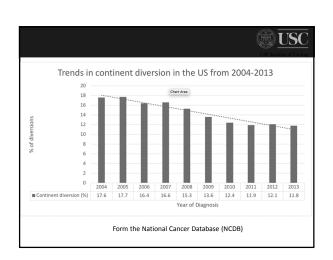


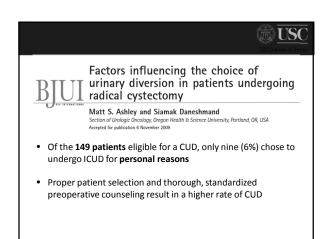
Likelihood of continent diversion: (multivariate analysis)

- Inversely associated with
  - older age
  - African American race
  - higher comorbidity index
- Directly associated with
  - male sex
  - higher education level
  - year of surgery
  - academic and NCI-designated cancer centers
  - high-volume providers

### Frequency of urinary diversion by continent reconstruction versus ileal conduit in selected series

AUTHOR	n	YEARS	SERIES	CONT	IC	OTHER**
Stein et al (2001)	634	1987- 1997	Univ. Southern California	93%	7%	0
Novotny et al (2006)	516	1993- 2005	Technical Univ., Dresden, Germany	36.8%	57.9%	5.2%
Kouba et al (2007)	102	2004- 2005	Univ. North Carolina	33%	67%	0
Gonheim et al (2008)	2,720	1970- 2000	Urology and Nephrology Ctr., Mansoura, Egypt	73%*	25%	2%
Daneshmand (2009)	188	2004- 2008	Oregon Health & Science Univ.	64%	35.5%	0.5%
Gore et al (2006)	3,611	1992- 2000	Nationwide. Medicare, SEER	19.9%	80.1%	0
Gore et al (2008)	5,075	1998- 2005	Nationwide. HCUP-NIS	14.3%	85.7%	0







UROLOGIC ONCOLOGY

Urologic Oncology: Seminars and Original Investigations 29 (2011) 473-47

News and topics
Choosing the right urinary diversion: Patient's choice or surgeon's inclination?

E.C Skinner, M.D.

- "At least 2/3 of patients presenting for cystectomy are likely to be reasonable candidates for some sort of continent urinary diversion.
- "The vast majority of patients will opt for a continent diversion if the pros and cons of each type of diversion are presented in a balanced

# Patient/Urinary Diversion Selection



- Advantages of Ileal Conduit Urinary Diversion
  - Shorter operative time
  - Ease of care by others
  - Easier to learn

#### Disadvantages

- Requirement of external appliance
- Impairment of body image
- Herni
- Skin irritation

#### Contraindications for Orthotopic Neobladder



- Compromised renal function (Cr >1.8, Cr clearance >45)
- Severe hepatic dysfunction
- Compromised intestinal function
- Positive urethral margin
- Mental impairment
- Pre-existing incontinence
- Pelvic radiation (increased complications)
- Recurrent urethral stricture disease
- AGE NOT CONTRAINDICTION!!

# **Renal Function**



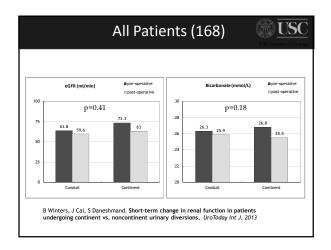
- 168 total cases
  - 44 Ileal conduit
  - 109 Studer orthotopic ileal neobladder
  - 15 Continent cutaneous diversion
    - right colon pouch via Monti or appendicoumbilicostomy
- Pre-existing renal insufficiency (RI) vs. normal:
  - 58 with insufficiency (eGFR < 60 ml/min)
  - 110 normal

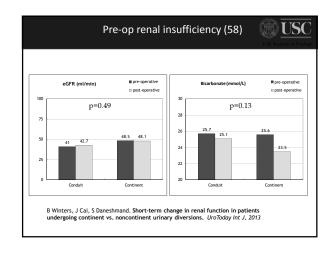
B Winters, J Cai, S Daneshmand. Short-term change in renal function in patients undergoing continent vs. noncontinent urinary diversions. UroToday Int J, 2013

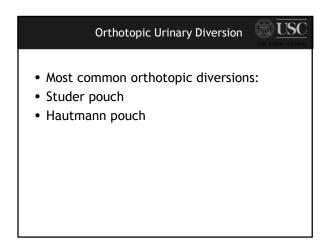
# Renal Function B Winters, J Cal, 5 Daneshmand. Short-term change in renal function in patients undergoing continent vs. noncontinent urinary diversions. *Diol Today in J.* 2013

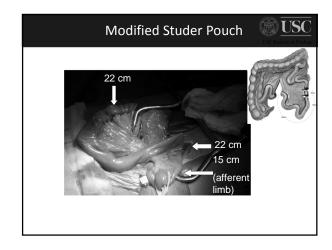
Summary table	Conduit	Continent	Significance
Average Age	71.4	65.3	p<0.001
Mean pre-op eGFR	63.8	73.3	p<0.001
Preexisting RI (58)	24 (41%)	34 (59%)	
Mean pre-op eGFR with Renal insufficiency	41	48.5	p=0.009
	Conduit	Continent	
Mean f/u for all	17.5	19.9	p=0.10
Median f/u for all	16 months (	range 3-60)	

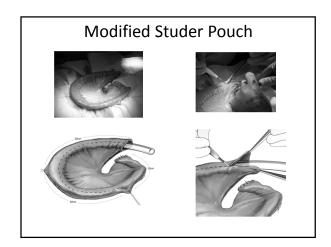
B Winters, J Cai, S Daneshmand. Short-term change in renal function in patients undergoing continent vs. noncontinent urinary diversions. *UroToday Int J., 2013* 

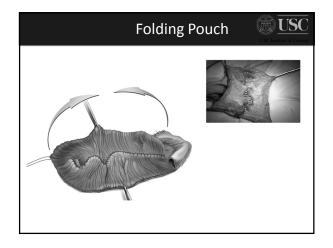


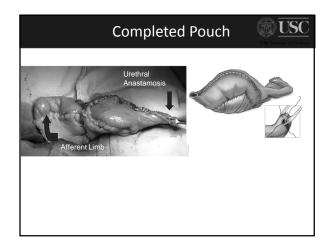


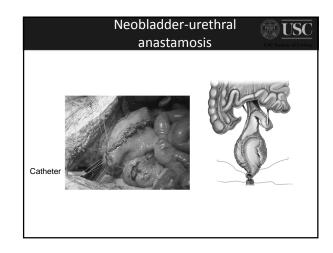


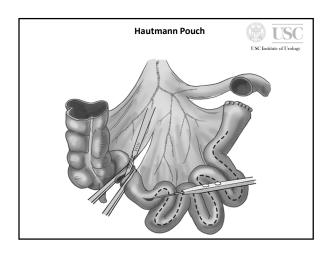


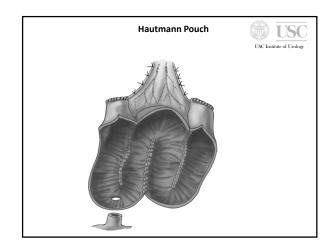


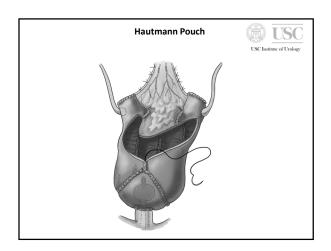


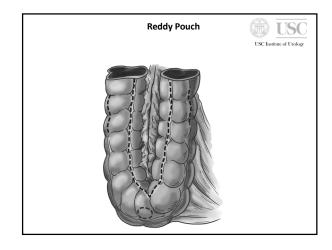


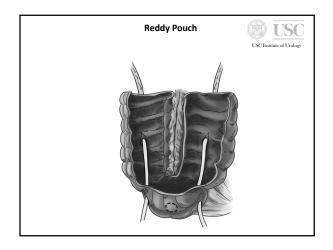


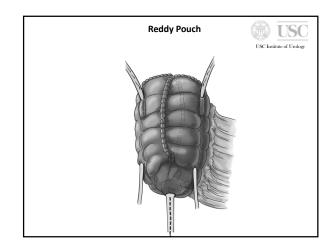


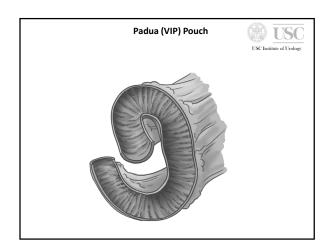


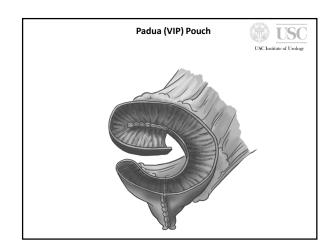


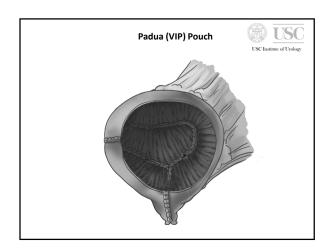


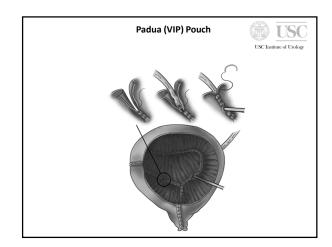


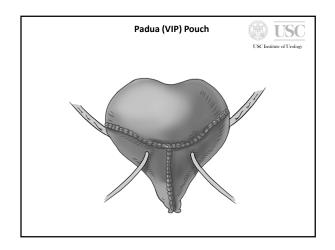


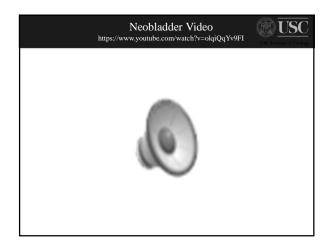


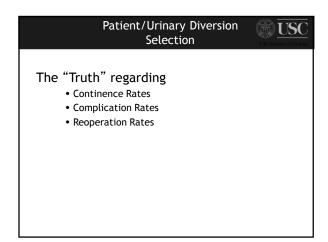


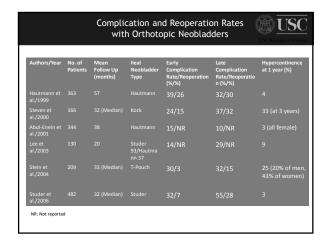


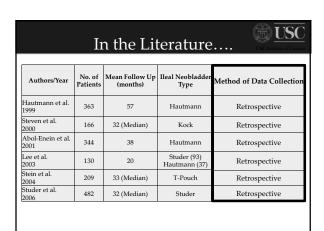


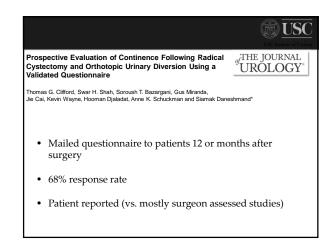


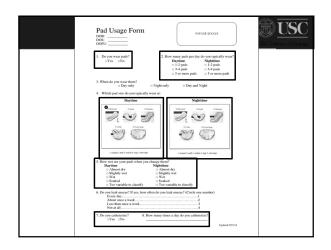




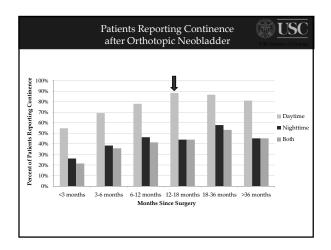


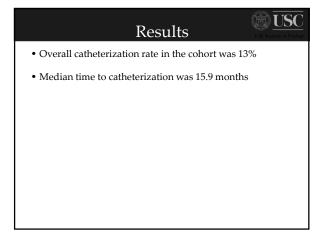




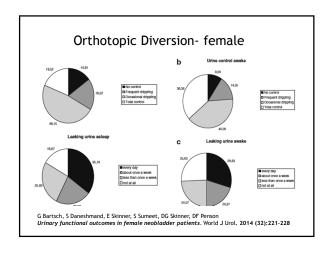


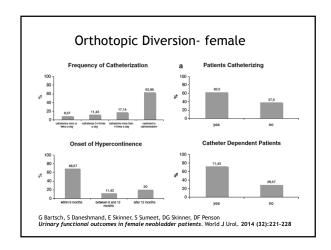
# Patients underwent RC between 2000 and 2014 Patients underwent RC between 2000 and 2014 1545 patients 153 male patients with available questionnaires 284 pad usage questionnaires were collected 243 interval distinct questionnaires were defined

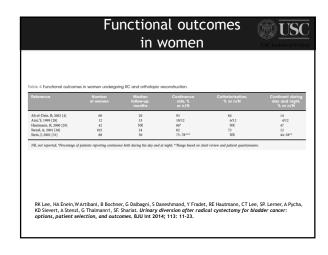


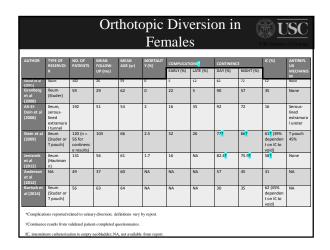


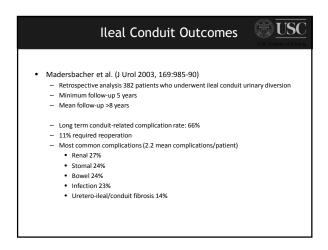




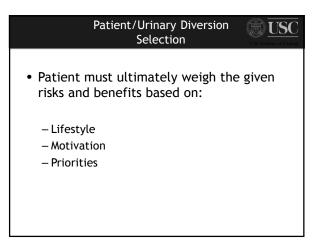




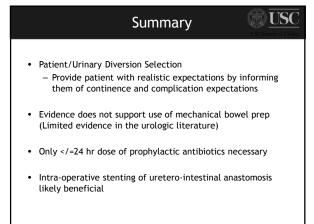


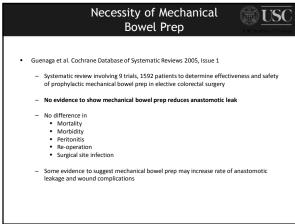


# Quality of Life Studies on Urinary Diversion • Extensive literature, generally low scientific quality • Published evidence - No difference in QOL when comparing: • Continent cutaneous and conduit • Neobladder and conduit • Continent cutaneous and neobladder • Neobladder, continent cutaneous, and conduit - Difficult study design

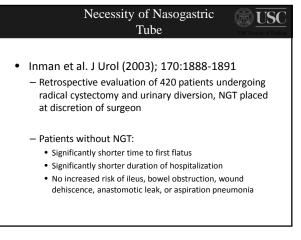


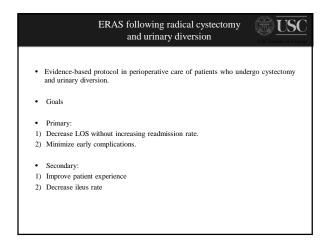
	rinary diversion ce 2000				
References	Instrument	No. Pts	Year	Population	Findings
McGuire et al	SF-36	76	2000	United States	Lower mental QOL scores in IC patients compared to populationorm
Fujisawa et al	SF-36	56	2000	Japan	No differences detected between groups
Hobish et al	EORTC-QLQ-C30	102	2000	Austria	Higher QOL scores in NB patients
Hara et al	SF-36 + informal questionnaire	85	2002	Japan	No differences detected in general HRQOL
Dutta et al	SF-36 FACT-G	100	2002	United States	Marginally higher HRQOL scores detected in NB group
Protogerou et al	EORTC-QOL-C30, informal questionnaire	108	2004	Greece	Urinary and sexual function impairments present following cystectomy but no HRQOL differences between groups
Kikuchi et al	FACT-BL	35	2006	Japan	Lower body image scores among ileal conduit patients
Gilbert et al	BCI	315	2007	United States	Decreased urinary HRQOL among NB group
Saika et al	EORTC-QLQ-C30	78	2007	Japan	No significant difference between IC and NB
Autorino et al	SF-36	79	2008	Italy	No difference between IC and NB, but physical, emotional and social QOL scores below population norm
Sogni et al	EORTC-QLQ-C30 + EORTC-QLQ-BLM30	34	2008	Italy	Global health status higher in NB group but not significant
Philip et al	SF-36, informally developed questionnaire	52	52	England	NB group had significantly better physical functioning
Somani et al	EORTC-QLQ-C30 + SWLS	32	2009	England	No HRQOL difference before or after cystectomy
Hedgepeth et al	BCI	224	2010	United States	No difference between IC and NB groups
Erber et al	EORTC-QLQ-C30 + EORTC-QLQ-BLM30	58	2012	Germany	Higher HRQOL scores among NB vs. IC patients
Gacci et al	EORTC-QLQ-C30 + EORTC-QLQ-BLM30, FACT-BL	25	2013	Italy	No HRQOL differences among female patients
Metcalfe et al	FACT-VCI	84	2013	Canada	No HRQOL differences between IC and NB groups
Singh et al	EORTC-QLQ-C30	164	2014	India	General HRQOL better in NB group compared to IC group
Huang et al	BCI	294	2015	China	No difference in long-term HRQOL between IC and NB

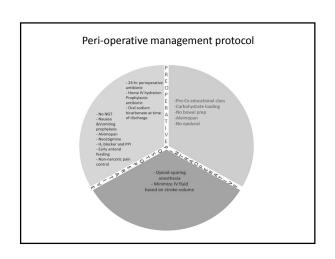










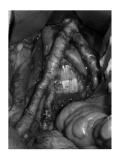


#### **ERAS**

- Smaller incision
- Less bowel manipulation and efficient and expeditious surgery
- Minimization of blood loss and transfusion
- Consistency



# "super extended PLND"





#### **ERAS**

#### Preservation of gastrointestinal function

- Carbohydrate loading.
- Pharmacological prophylaxis of postoperative nausea or vomiting
- Avoidance of NG tubes
- Avoidance of bowel preparation
- Enforced early enteral feeding- "cystectomy" diet on POD#1
- Liberal use of laxatives.
- Alvimopan

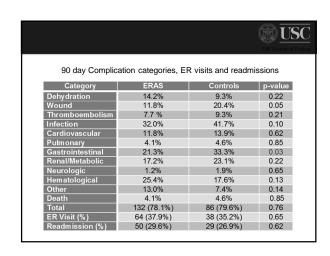
## **ERAS**

#### Active pain control

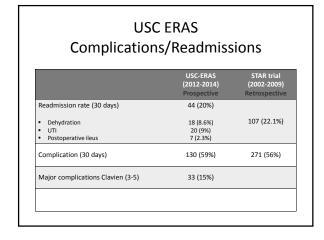
- 1. Non-narcotic analgesia initiated intraoperatively.
- 2. Opioids for breakthrough pain
- 3. Instillation of local anesthetic catheters at incision sites.

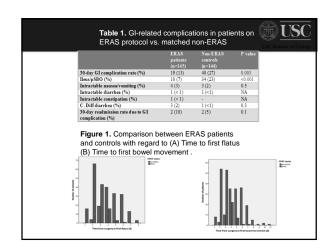
# Enhanced Recovery Protocol after Radical Cystectomy for Bladder Cancer Siamak Daneshmand,\*,† Hamed Ahmadi, Anne K. Schuckman,‡ Anirban P. Mitra, Jie Cai, Gus Miranda and Hooman Djaladat From the Institute of Urbay, Notes Complemente Care and Department of Pathology and Center for Personalized Medicine (APM), University of Southern California Les Aegoles, California Hospital Stay Significant Control of Cancer (Cancer and Department of Pathology and Center for Personalized Medicine (APM), University of Southern California Les Aegoles, California Hospital Stay Significant Control of Cancer (Cancer and Department of Pathology and Center for Personalized Medicine (APM), University of Southern California Les Aegoles, California B ERAS Patients Historical Cohort Significant Cohort (Cancer Cancer and Department of Pathology and Center for Personalized Medicine (APM), University of Southern California Les Aegoles, California B ERAS Patients Historical Cohort (Cancer Cancer and Department of Pathology and Center for Personalized Medicine (APM), University of Southern California Les Aegoles, California B ERAS Patients Historical Cohort (Cancer Cancer and Department of Pathology and Center for Personalized Medicine (APM), University of Southern California Les Aegoles, California (Cancer Cancer and Department of Pathology and Center for Personalized Medicine (Cancer Cancer and Department of Pathology and Center for Personalized Medicine (Cancer Cancer and Department of Pathology and Center for Personalized Medicine (Cancer Cancer and Department of Pathology and Center for Personalized Medicine (Cancer Cancer Cancer and Department of Pathology and Center for Personalized Medicine (Cancer Cancer Cancer and Department of Pathology and Center for Personalized Medicine (Cancer Cancer Cancer and Department of Pathology and Center for Personalized Medicine (Cancer Cancer Cance

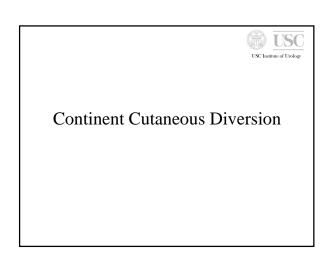
ι	USC ERAS (Updated results)							
Patients	USC-ERAS Open RC (2012–2014)	STAR trial (2002-2009)	USC modern era (2003-2009)					
No. (M/F)	377 (169/52)	484 (411/73)	557 (433/124)					
Age	69 (31-90)							
Neoadjuvant chemo	98 (35%)							
Diversion type	ONB: 173 (62%) CCD: 14 (7%) IC: 75 (34%)	ONB	ONB: 448 (80%) CCD: 23 (5%) IC: 85 (15%)					
EBL (median)	400 cc							
Median time to BM (d)	2							
Median LOS (d)	4 (3-24)	8 (0-70)	9 (4-62)					



#### Postoperative Pain Management after Radical Cystectomy: **Comparing Traditional versus Enhanced Recovery Protocol** rom the Institute of Urology, Norris Comprehensive Cancer Center, University of Southern Califo ERAS Traditional p-value Total number of patients Median age (years) 71 70 27 (21.8) 18 (22.2) Female sex (%) Charlson comorbidity index (number of pts) 27 20 0.7 ≥2 41 23 Pathologic organ confined cancer (%) 79 (63.7) 52 (64.2) Median surgery length (min) Median estimated blood loss (mL) 350 360 0.2 400 600 0.0001 <0.0001 <0.0001 Length of hospital stay (day) 4.9 20.67 Mean morphine equivalent use (mg/day) Total morphine equivalent use (mg) 24.08 <0.0001 Mean pain VAS score/ day < 0.0001 3.1 1.14 Postoperative Ileus (%) J Urol, Vol. 194, 1209-1213, November 2015 9 (7.3) 18 (22.2) 0.0028







# Patient/Urinary Diversion Selection • Advantages of continent cutaneous urinary diversion - High total (day and night) continence rate - Immediate continence - No need for external appliance • Disadvantages of a continent cutaneous urinary

- Need for regular catheterization

diversion

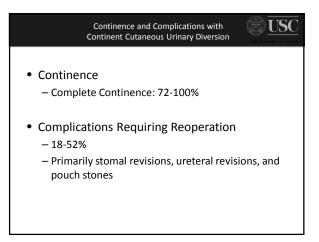
- Risk for reoperation for complications

# Continent Cutaneous Diversion Indications - Urinary Incontinence - Urethral stricture - Positive urethral margin - ? Prior Pelvic Radiation

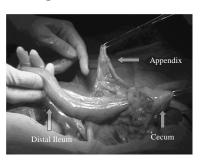
# Continence Mechanism USC Ileocecal Valve (Indiana Pouch) Tapered Ileum Appendix (buried in subserosal tunnel)

Authors	Year	No. Pts	Mean Follow Up (mos)	Urinary Diversion Type	Daytime and Nighttime continence (%)
Bihrle R	1997	50	30 (minimum)	Indiana	94
Stein et Daneshmand	2004	27	33	Penn	100
Wiesner et al.	2006	401	95	Mainz I/Right Colon	87
Holmes et al.	2002	125	41	Indiana	72
Webster et al.	2003	74	133	Florida	93

Authors	Year	No. Pts	Follow Up (mos)	Urinary Diversion Type	Complication Requiring Surgical Intervention (%)	Stomal Complications (% of total patients)
Bihrle R	1997	50	30 (minimum)	Indiana	18	6
Stein et Daneshmand	2004	27	33 (mean)	Penn	33	28
Wiesner et al.	2006	401	95 (mean)	Mainz I/Right Colon	>51	36
Holmes et al.	2002	125	41	Indiana	52	14
Webster et al.	2003	74	133	Florida	39	12



Right Colon Pouch



Right Colon Pouch



**Right Colon Pouch** 



25cm segment of right colon isolated

Right Colon Pouch



Isolated segment of bowel for pouch

# Right Colon Pouch



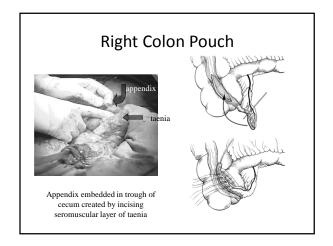
Appendiceal tip cut to allow 12-16F Catheter

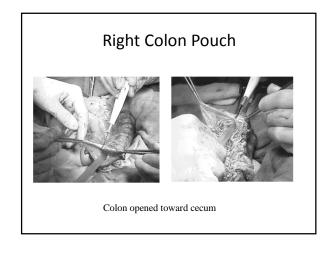
# Right Colon Pouch

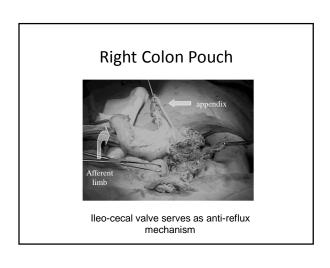


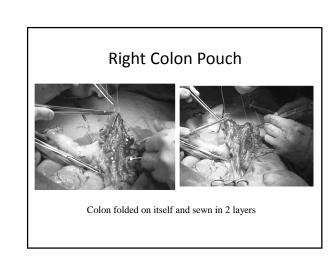


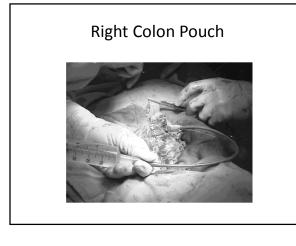
Two-layered hand sewn ileo-colic anastamosis

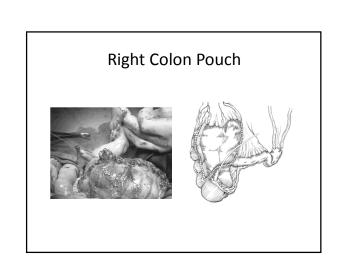


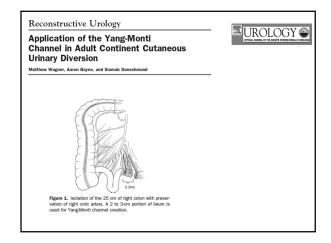


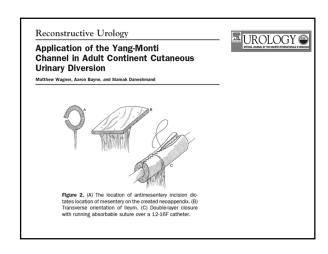


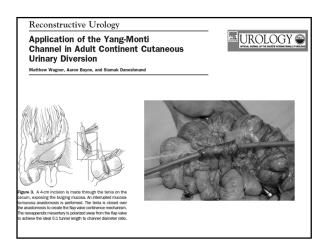


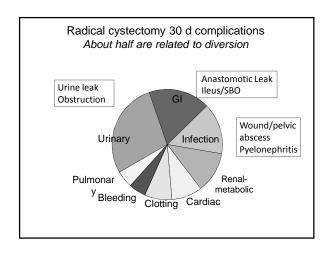






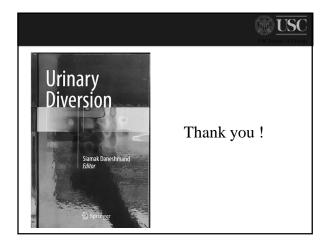


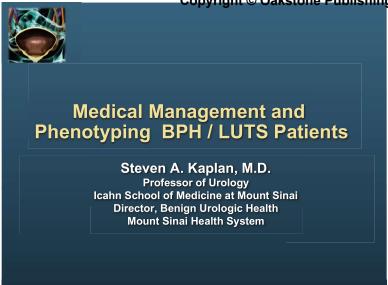




# Early diversion-related complications management GI complications Urine leak Pelvic abscess, infected lymphocele UTI/sepsis Management of late complications by diversion type Ureteroileal strictures Parastomal hernia Pouch stones Incontinence Difficulty catheterization/stoma stenosis

# Most common early complication Most are not serious but are aggravating Can minimize with ERAS techniques Diarrhea/constipation/nausea manage with OTC meds rule out C.Diff if diarrhea persists > 2 d may cause dehydration – require support/readmission Bowel anastomosis leak 1-2% often subtle, difficult to diagnose may lead to fistula, pelvic abscess, ureteral obstruction Can avoid with careful technique percutaneous drains, bowel rest rarely need to re-operate except for severe leak, rectal injury or refractory SBO





# Disclosure:

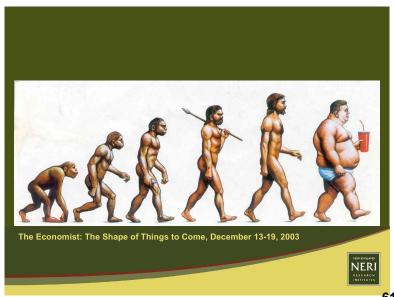
Dr. Kaplan has nothing to disclose.



# Male Pelvic Health

New Terminology, New Concepts, Better Choices

Significance of obesity and the metabolic syndrome



# Obesity Trends\* Among U.S. Adults BRFSS, 1985

(\*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



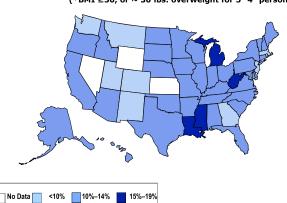
No Data <a><10%</a> 10%-14%

Source: Behavioral Risk Factor Surveillance System, CDC.



# Obesity Trends\* Among U.S. Adults **BRFSS, 1991**

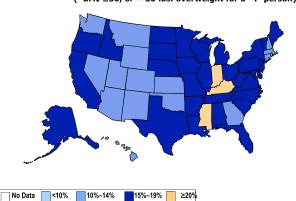
(\*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.

# Obesity Trends\* Among U.S. Adults **BRFSS, 1997**

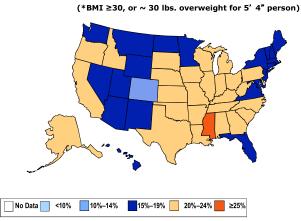
(\*BMI ≥30, or ~ 30 lbs. overweight for 5' 4" person)



Source: Behavioral Risk Factor Surveillance System, CDC.



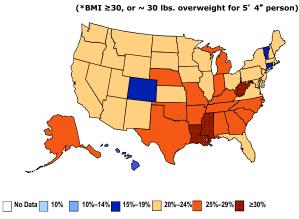
# Obesity Trends\* Among U.S. Adults **BRFSS, 2001**



Source: Behavioral Risk Factor Surveillance System, CDC.

25-29

# Obesity Trends\* Among U.S. Adults **BRFSS, 2005**



Source: Behavioral Risk Factor Surveillance System, CDC.

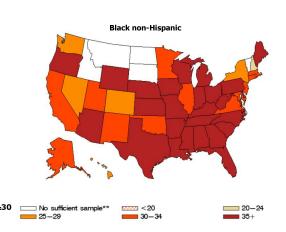


# State-specific Prevalence of Obesity\* Among U.S. Adults, by Race/Ethnicity, 2006-2008

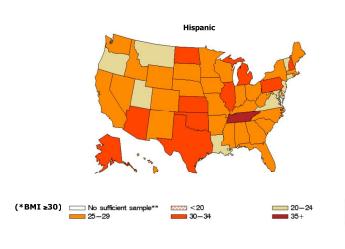
White non-Hispanic

# **ODC**

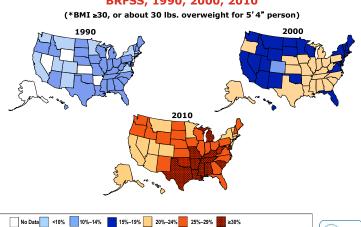
# State-specific Prevalence of Obesity\* Among U.S. Adults, by Race/Ethnicity, 2006-2008



# State-specific Prevalence of Obesity\* Among U.S. Adults, by Race/Ethnicity, 2006-2008



#### Obesity Trends\* Among U.S. Adults BRFSS, 1990, 2000, 2010

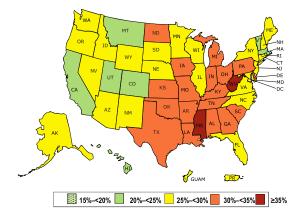


Source: Behavioral Risk Factor Surveillance System, CDC



# Prevalence\* of Self-Reported Obesity Among U.S. Adults by State and Territory, BRFSS, 2013

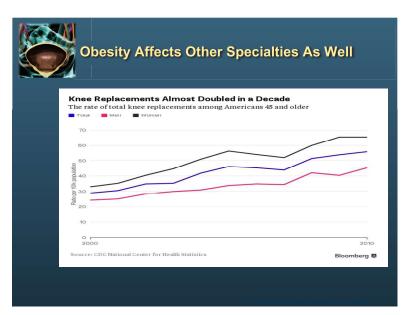
\*Prevalence estimates reflect BRFSS methodological changes started in 2011. These estimates should not be compared to prevalence estimates before 2011.



Source: Behavioral Risk Factor Surveillance System, CDC.



**CDC** 



## Treatments for LUTS, BPH, BOO

- Watchful waiting1,2
- Medical therapy<sup>2,3</sup>
  - Phytotherapy
  - α-adrenoreceptor (AR) blockers
  - 5-α reductase inhibitors
  - Antimuscarinic agents
  - PDE 5 inhibitors
- Combination therapy
- Office-based treatment<sup>2,3</sup>
  - TUMT (transurethral microwave thermotherapy)
  - TUNA (transurethral needle ablation)
  - Botulinum toxin type A injection
  - Experimental treatments

- Surgicenter/ hospital-based treatment2,3
  - TURP (transurethral resection of the prostate; gold standard)
  - TUIP (transurethral incision of the prostate)
  - Open surgery (prostatectomy)
  - TUVP (transurethral electrovaporization ablation of the prostate)

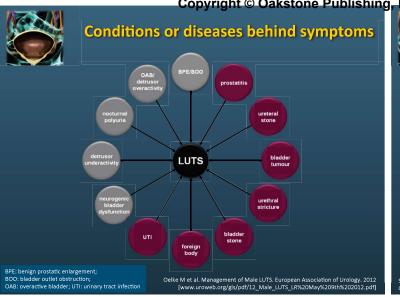
Phytotherapy  $\alpha$ -adrenoreceptor (AR) blockers 5- $\alpha$  reductase inhibitors Antimuscarinic agents PDE - 5 inhibitors Combination therapy

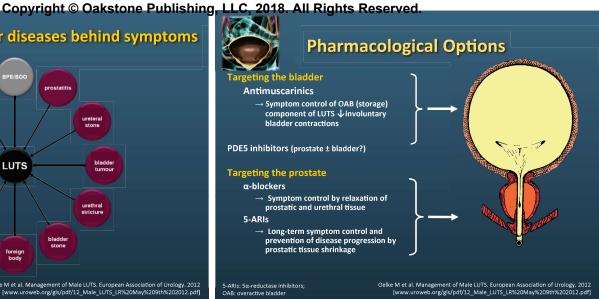
# Male LUTS

# **Identification of Patient Profile**

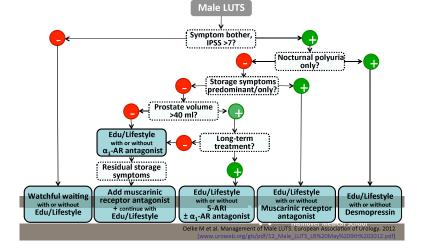
- -Who has BPH?
- -Who should be treated?
- -What is the optimal treatment for each patient?

Chatelain C et al. In: Chatelain C et al, eds. Benign Prostatic Hyperplasia. Plym
 2001;519-534.
 McConnell JD et al. Benign Prostatic Hyperplasia: Diagnosis and Treatment. B
 Care Policy and Research. 1994. AHCPR Publication No. 94-0582.
 Drelkom K et al. In: Chatelain C et al, eds. Benign Prostatic Hyperplasia. Plymouth, UK: Health of Call (2001;479-511).





# **Treatment Algorithm Male LUTS: Drugs**



#### α-Blockers for Treatment of BPH

- Most commonly used and effective medical therapy for treating LUTS secondary to BPH1
- Prevents clinical symptomatic progression of BPH<sup>1</sup>
- Efficacious<sup>2</sup>
- Well tolerated
- Reduce the cost of medical therapy<sup>3</sup>
- 1 IMS HEALTH NPA 2008
- MS REALTH NPA 2006.
   McConnell JD et al. N Engl J Med. 2003;349;2387-2398.
   Naslund M et al. Am J Manag Care. 2007;13(suppl 1):S17-S22.

# Efficacy of alpha1 - blocker

	α₁-AR antagonist
Total IPSS	↓ 35 - 40%
Q <sub>max</sub>	↑ 20 <b>-</b> 25%
Onset of action	Rapid (days)
Prostate volume	-
Long-term risk of AUR or BPH-related surgery	-

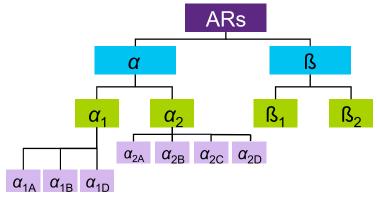
AUR: acute urinary retention:

BPH: benign prostatic hyperplasia;

IPSS: International Prostate Symptom Score:

Q<sub>max</sub>: maximum urinary flow rate

# Adrenoreceptor (AR) Subtypes



Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12\_Male\_LUTS\_LR%20May%209th%202012.pdf]



# α₁ Adrenoreceptor Distribution & Function







Primary subtype expressed in the prostate. Regulates contraction of the smooth muscle in the prostate, bladder base and neck urethra, seminal vesicles, and vas deferens.1-5

- Schwinn DA, et al. Int J Urol. 2008;15:193-199.
   Kaplan SA. Urology. 2004;63:428-434.
   Nasu K, et al. Br J Pharmacol. 1996;119:797-803.
   Murata S, et al. J Urol. 2000;164:578-583.

# $\alpha_{1D}$

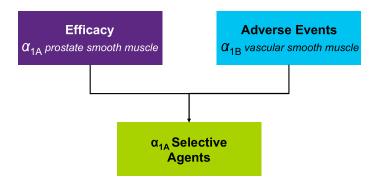
Primary subtype expressed in the bladder, spinal cord, and nasal passages. Thought to play a role in bladder symptoms. Regulates nasal secretions.

#### $\alpha_{1B}$

Primary subtype expressed in the blood vessels in response to postural redistribution of blood volume.4-7

- Carbone DJ, et al. Int J Impotence Res. 2003;15:299-306.
   Stafford-Smith M, et al. Can J Anesth. 2007;54:549-555.
   Townsend SA, et al. Hypertension. 2004;44:776-782.

# Assumptions in 1990s Driving Development of α-Blockers for BPH



Roehrborn CG, Schwinn DA. J Urol. 2004;171:1029-1035

# **New Concepts in Drug** Development of α-Blockers

# α<sub>1</sub>-ARs and Human LUTS

α <sub>1B</sub> >	Prostate	Spinal Cord	Detrusor	Vessels
$\alpha_{1A}$ $\alpha_{1D}$ $\alpha_{1D}$ $\alpha_{1A}$	α <sub>1A</sub>	α <sub>1D</sub>	α <sub>1D</sub>	α <sub>1B</sub> > α <sub>1A</sub>

- - $\alpha_{1A}$  ARs in bladder neck and prostate
- **↓** LUTS
  - $\hspace{0.1in} \alpha_{1A}$  in bladder neck and prostate smooth muscle
  - α<sub>1D</sub> in bladder
  - $\,\alpha_{1D}$  in sensory afferents and central nervous system
- - α<sub>1B</sub> in blood vessels

Roehrborn CG, Schwinn DA. *J Urol.* 2004;171:1029-1035 Schwinn DA, Roehrborn CG. *Int J Urol.* 2008;15:193-199.

# α-Adrenergic Selectivity of BPH Drugs

Study Type	Assessment
Pharmacologic	Receptor binding studies
Uroselectivity	Relative potency for inhibiting prostate vs vascular smooth muscle (in vitro studies)
Clinical	Efficacy vs adverse events in RCT

RCT, randomized, controlled trial.

# Pharmacologic Selectivity Profiles of α-Blockers

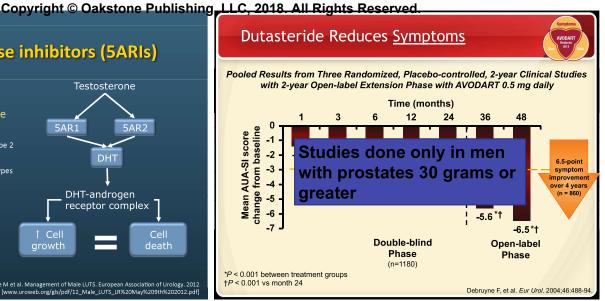
α₁-Blocker	α <sub>1</sub> -Receptor Selectivity
Doxazosin <sup>1</sup>	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Terazosin <sup>1</sup>	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Alfuzosin <sup>1</sup>	$\alpha_{1A} = \alpha_{1D} = \alpha_{1B}$
Tamsulosin <sup>1,2</sup>	$\alpha_{1A} = \alpha_{1D} > \alpha_{1B}$
Silodosin <sup>3</sup>	$\alpha_{1A} > \alpha_{1D} > \alpha_{1B}$

Results based on in vitro data

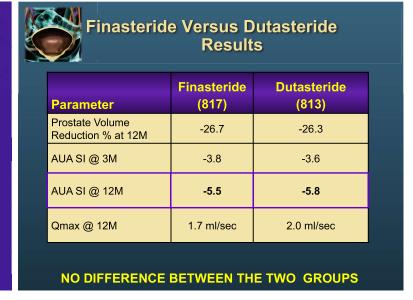
# Alpha-blocker Competitive Efficacy Review

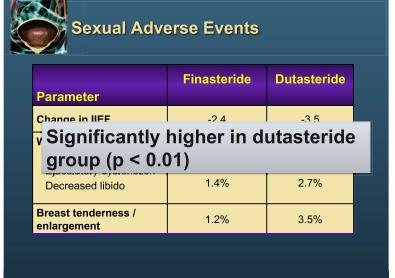
Schwinn DA, et al. *Mayo Clin Proc.* 2004;79:1423-1434.
 Kenny BA, et al. *Br J Pharmacol.* 1996;118:871-878.
 Akiyama K, et al. *J Pharm Exp Ther.* 1999;291:81-91.

 $5\alpha$ -reductase inhibitors (5ARIs) For long-term use in men with Testosterone enlarged prostates Exert an androgen effect on the prostate: Finasteride: inhibits 5α-reductase type 2 only Dutasteride: inhibits 5α-reductase types 1 and 2 DHT-androgen Act to reduce serum DHT receptor complex concentrations Long half-life for dutasteride: Finasteride: 6-8 hours Dutasteride: 3-5 weeks



A 5 Year Study Of 5 - Alpha Reductase Inhibitors In Men With Benign Prostatic Hyperplasia: Finasteride **Has Equal Efficacy And Prostate Volume Reduction But Has Less Sexual Side Effects And Breast Enlargement Than Dutasteride** Steven A. Kaplan, Doreen E. Chung, Richard K. Lee, Scott Melamed, Alexis E. Te Weill Cornell Medical College **Cornell University** 





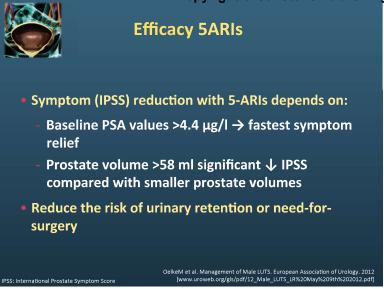


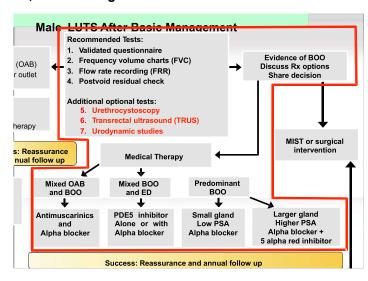
# **Efficacy 5ARIs**

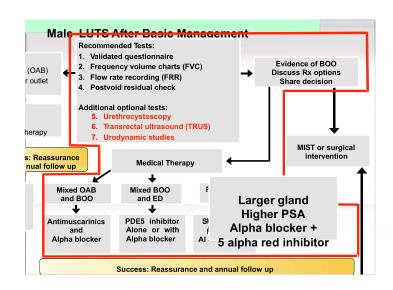
Clinical effects are observed after a minimum treatment period of 6-12 months; therefore, long-term treatment necessary

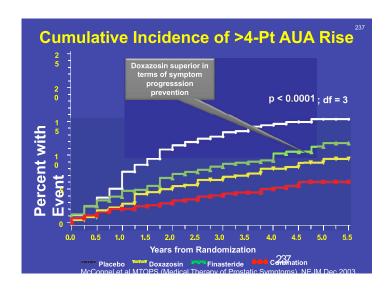
- After 2–4 years of treatment, IPSS is reduced by ~15–30% and prostate size ↓by 20-30%
- Symptom reduction (IPSS) is dependent on prostate size at treatment initiation
- In men with prostate sizes <30-40 ml efficacy is comparable</li> with placebo

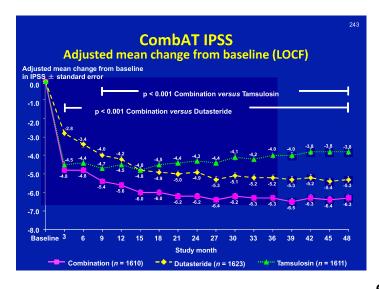
OelkeM et al. Management of Male LUTS. European Association of Urology. 20 [www.uroweb.org/gls/pdf/12\_Male\_LUTS\_LR%20May%209th%202012.p

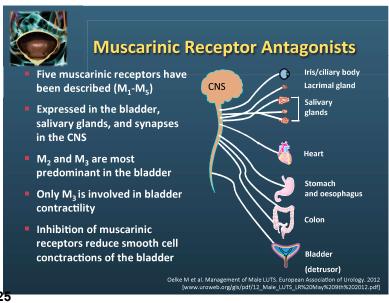




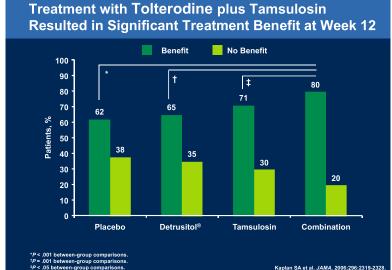


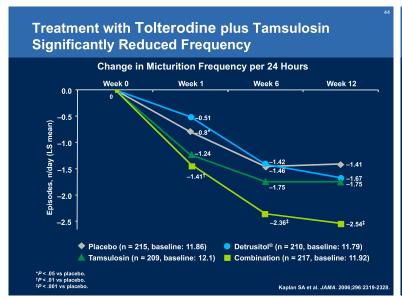


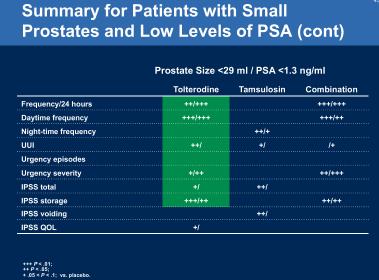




Copyright © Oakstone Publishing, LLC, 2018. All Rights Reserved. Most Men with LUTS Have Both Storage and Voiding/Post-micturition Symptoms Symptoms Relate micturition to the Bladder Symptoms Relate to the Prostate · Slow stream Frequency Straining Symptoms of both Terminal dribble Urgency urinary OAB and BPH Post-micturition dribble Incomplete emptying OAB is defined as urgency, with or without urgency incontinence. usually with frequency and nocturia (ICS 2002 definition). rwin DE et al. Eur Urol. 2006;50:1306-1315 Abrams P et al. Urology, 2003:61:37-49



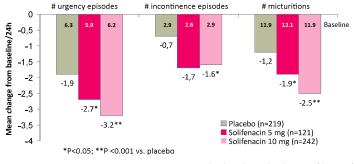




### **Summary for Patients with Large Prostates and High Levels of PSA (cont)** Prostate Size ≥29 ml / PSA ≥1.3 ng/ml Tamsulosin Tolterodine Combination Frequency/24 hours Daytime frequency Night-time frequency ++/+ **Urgency episodes** +++/++ +++/+++ **Urgency severity IPSS total** +/+++ +++/+++ IPSS storage IPSS voiding IPSS QOL ++/++

# **Efficacy Antimuscarinics in Male LUTS**

Meta-analysis: subgroup analysis of 582 men from 4 RCTs (phase III) evaluating the efficacy and safety of solifenacin (12 weeks) in male OAB patients (n=2,848)



RCT: randomised controlled trial; OAB: overactive bladder

van Kerrebroeck P et al. Eur Urol Suppl 2005; 4: 61 (abstract 233) Chapple CR et al. Int J Clin Pract 2006; 60: 959 - 966

Oelke<sup>6</sup>

# **Antimuscarinics ONLY in Male LUTS**

Trials	Duration (weeks)	Treatment	Patients [N]	Voiding frequency [%]	Nocturia [%]	Urgency Incontinence [%]	IPSS [%]	LE									
Kaplan et al. (2005)	25	Tolterodine 1 x 4mg/d (after α-blocker failure)	43	-35.7 °	-29.3 °	- [20]	-35.5°	2b									
Roehrborn et al.	12	Placebo	86	-4	-	-40	-	1b									
(2006)		Tolterodine 1 x 4mg/d	77	-12	-	-71 *	-										
Kaplan et al.	12	Placebo	374	-7.9	-17.6	-	-	1b									
(2006)		Tolterodine 1 x 4mg/d	371	-10.8 *	-18.8	-											
Kaplan et al.	12	Placebo	215	-13.5	-23.9	-13	-44.9	1b									
(2006)											Tolterodine 1 x 4mg/d	210	-16.5	-20.1	-85 *	-54	
Dmochowski et	12	Placebo	374	-5.6	-17.6	-	-	1b									
al. (2007)		Tolterodine 1 x 4mg/d	371	-8.7	-18.8	-	-										
Höfner et al. (2007)	12	Tolterodine 1 x 4mg/d	741	-20 ª	-42.9 ª	-100	-37.9 °	2b									
Herschorn et al.	12	Placebo	124	-10.2	-	59.3	-	1b									
(2009)		Fesoterodine 1 x 4mg/d	111	-13.2 *	-	-84.5 *											
		Fesoterodine 1 x 8mg/d	109	-15.9 *	-	-100 *	-										

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12\_Male\_LUTS\_LR%20May%209th%202012.pdf]

# **PVR and Urinary Retention**

-Monotherapy Antimuscarinics-

TRIAL	Duration [weeks]	Treatment	Patients [N]	PVR [ml]	Rento N	ention %
Kaplan et al. 2005	25	Tolterodine 1x4 mg/d	43	- 22*	0	0
Roehrborn et al. 2006	12	Placebo	86		0	0
		Tolterodine 1x4 mg/d	77		1	1.3
Kaplan et al. 2006	12	Placebo	374		2	0.5
		Tolterodine 1x4 mg/d	371		3	0.8
Kaplan et al. 2006	12	Placebo	215	- 3.6	3	1.4
		Tolterodine 1x4 mg/d	210	+ 5.3	2	0.9
Dmochowski et al. 2007	12	Placebo	374		2	0.5
		Tolterodine 4 mg/d	371		4	1.1
Höfner et al. 2007	12	Tolterodine 1x4 mg/d	741	0	8	0.7
Chapple et al. 2009	12	Placebo	323	+1,1	6	1.9
		Tolterodine 1x4 mg/d	329	+ 14.3 *	6	1.8
Herschorn et al. 2010	12	Placebo	124		1	0.8
		Fesoterodine 1x4 mg/d	120	+ 9.6**	1	0.8
		Fesoterodine 1x8 mg/d	114	+ 20.2**	6	5.3

\* P=0.023 \*\*P=0.035

PVR: post-void residual

Adapted from Oelke M. UniMed Science. Hampel (Ed) 2009 pp84 - 97 Herschorn S et al. Urology 2010: 75; 1149 - 55

# Other OAB Monotherapies

- Beta 3 adrenoreceptor agonist- Mirabegron
  - No significant urodynamic changes in men
  - Symptom improvement at 50 mg dosage
- PD5 Inhibitor Tadlafil
  - Significant symptom improvement with improved erectile function
  - No urodynamic impact/effect/changes
  - Sounds like OAB Rx

/ et al., J Urol. 2013 Oct;190(4):1320-7. ci H, et al. Int Urol Nephrol. 2013 Feb;45(1):53-80. winkel W et. Clin Ther. 2012 Oct;45(10):2144-60 rbom OC et al., J Urol. 2013 Oct;25:50022-2347(13)05757-1. M et. Res Rep Urol. 2013 Apr. 65:99-111 H.et al., J Sex Med. 2013 Aug;10(8):2044-52.

Oelke<sup>©</sup>

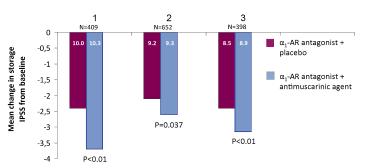
# **Combination Therapy**

- α-blockers + muscarinic receptor antagonists:
  - Inhibit both α-adrenoceptors and muscarinic cholinoreceptors

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12\_Male\_LUTS\_LR%20May%209th%202012.pdf]

# Addition of an antimuscarinic to an $\alpha_1$ -blocker improves persistent storage symptoms

12-week, double-blind RCTs in men  $\geq$ 40 or 45 yr with OAB symptoms after  $\geq$ 4 w on  $\alpha_1$ -AR antagonist  $Q_{max} \ge 4$  or 5 ml/s; PVR  $\le 200$  ml (type of active agents differs between studies)



<sup>1</sup> MacDiarmid SA et al. Mayo Clin Proc 2008; 83: 1002 - 1010 <sup>2</sup>Chapple C et al. Eur Urol 2009; 56: 534 - 543 <sup>3</sup> Kaplan SA et al. J Urol 2009; 182: 2825 - 2830 Oelke®

# α<sub>1</sub>-blocker + Antimuscarinic

Trials	Duration (weeks)	Treatment (daily dose)	Patients [N]	Voiding frequency [%]	Nocturia [%]	IPSS [%]	LE
Saito et al.	4	Tamsulosin 1 x 0.2 mg/d	59	-29.6	-22.5		1b
(1999)		Tamsulosin + propiverine 1 x 20 mg/d	75	-44.7	-44.4 <sup>a</sup>		
Lee et al.	8	Doxazosin 1 x 4 mg/d	67	-11.8	-37.5	-54.9	1b
(2005)		Doxazosin + propiverine 1 x 20 mg/d	131	-27.5 <sup>a</sup>	-46.7	-50.7	
Kaplan et al.	12	Placebo	215	-13.5	-23.9	-44.9	1b
(2006)	(2006)	Tolterodine 1 x 4 mg/d	210	-16.5	-20.1	-54	
		Tamsulosin 1 x 0.4 mg/d	209	-16.9	-40.3	-64.9 *	
		Tolterodine + tamsulosin	217	-27.1 *	-39.9 *	-66.4 *	
MacDiarmid et	12	Tamsulosin 1 x 0.4 mg/d	209	-	-	-34.9	1b
al. (2008)		Tamsulosin + oxybutynin 1 x 10 mg/d	209	-	-	-51.9 *	
Kaplan et al. (2005)	25	Tolterodine 1 x 4 mg/d	43	-35.7 ª	-29.3 °	-35.3 °	2b
Yang et al. (2007)	6	Tolterodine 2 x 2 mg/d	33	-	-	-35.7 ª	2b
Kaplan et al.	12	Tamsulosin 1 x 0.4 mg/d + placebo	195	-6.2 <sup>a</sup>	-	-29	1b
(2009)		Tamsulosin 1 x 0.4 mg/d + solifenacin 5 mg/d	202	-9.1 <sup>8</sup>	-	-31.8	

The Health Improvement Network (THIN) **Database: Focused Safety Study of Acute Urinary Retention (AUR) in Men** 

Luis Alberto García-Rodríguez, Elisa Martín-Merino, Elvira Luján Massó-González, Claus G. Roehrborn

This study was funded by Pfizer Inc

# Relative Risk of Acute Urinary Retention by Antimuscarinic Timing of Use, Duration, and Daily Dose\*

	Number (%) of Patients					
	Cases (n=1844)	Controls (n=10,000)	RR†	95% CI		
Use Non-use	1706 (93)	9727 (97)	1			
Timing of use						
Current use	94 (5)	154 (2)	2.9	2.2-3.7		
Recent use	15 (<1)	39 (<1)	1.7	0.9-3.1		
Past use	29 (2)	80 (<1)	1.6	1.0-2.5		
Duration: Current use						
≤30 days	38 (40)	22 (14)	8.3	4.8-14.2		
31 days-1 year	28 (30)	60 (39)	2.0	1.2-3.1		
>1 year	28 (30)	72 (47)	2.0	1.3–3.1		
Daily dose/indication: Current use						
Low/medium dose	84 (89)	138 (90)	2.8	2.1-3.8		
High dose urogenital	10 (11)	16 (10)	3.0	1.3-6.8		

\*Percentages for timing of use are based on overall study cohort (1844 cases; 10,000 controls); percentages for duration and daily dose are based on the number of patients currently using antimuscarinics (94 cases, 154 controls). †Relative risk estimates were adjusted for age, calendar year, general practitioner visits, and oral antimuscarinic use.

# **PVR and Urinary Retention**

-Monotherapy Antimuscarinics-

TRIAL	Duration [weeks]	Treatment	Patients [N]	PVR [ml]	Rente N	ention %
Kaplan et al. 2005	25	Tolterodine 1x4 mg/d	43	- 22*	0	0
Roehrborn et al. 2006	12	Placebo	86		0	0
		Tolterodine 1x4 mg/d	77		1	1.3
Kaplan et al. 2006	12	Placebo	374		2	0.5
		Tolterodine 1x4 mg/d	371		3	0.8
Kaplan et al. 2006	12	Placebo	215	- 3.6	3	1.4
		Tolterodine 1x4 mg/d	210	+ 5.3	2	0.9
Dmochowski et al. 2007	12	Placebo	374		2	0.5
		Tolterodine 4 mg/d	371		4	1.1
Höfner et al. 2007	12	Tolterodine 1x4 mg/d	741	0	8	0.7
Chapple et al. 2009	12	Placebo	323	+ 1,1	6	1.9
		Tolterodine 1x4 mg/d	329	+ 14.3 *	6	1.8
Herschorn et al. 2010	12	Placebo	124		1	0.8
		Fesoterodine 1x4 mg/d	120	+ 9.6**	1	0.8
		Fesoterodine 1x8 mg/d	114	+ 20.2**	6	5.3

<sup>\*</sup> P=0.023 \*\*P=0.035

PVR: post-void residual

Adapted from Oelke M. UniMed Science. Hampel (Ed) 2009 pp84 - 97 Herschorn S et al. Urology 2010: 75; 1149 - 55

# **EAU Recommendations**

Furopean Association of Urology

#### Antimuscarinic monotherapy

Recommendations	LE	GR
Muscarinic receptor antagonists might be considered in men with moderate to-severe LUTS who have predominantly bladder storage symptoms	e- 1b	В
Caution is advised in men with bladder outlet obstruction	4	С

#### Antimuscarinic + $\alpha_1$ -blocker combination therapy

Recommendations	LE	GR
Combination treatment with a muscarinic receptor antagonist and an $\alpha_1$ -blocker and might be considered in patients with moderate-to-severe LUTS if symptom relief has been insufficient with monotherapy with either drug	1b	В
Combination treatment should be used cautiously in men suspected of having bladder outlet obstruction	2b	В

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12\_Male\_LUTS\_LR%20May%209th%202012.pdf]



# **Options/Recommendations:** Anticholinergics

Option:

Anticholinergic agents are appropriate alternatives for the management of LUTS/BPH in men without an elevated PVR and when LUTS are predominantly irritative.

Recommendations:

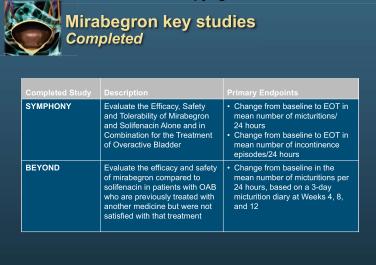
Prior to initiation of anticholinergic Rx, baseline PVR should be assessed.

Anticholinergics should be used with caution in men with PVR>250-300 mL.

**Based on Panel consensus** 

Mirabegron Primary Results Published in European Urology <del>o</del>au

AUA GUIDELINES



## Plant Extracts

Trials Duration (weeks)		Treatment	Patients (n)	Change in symptoms (IPSS) †	Change in Q <sub>max</sub> [mL/s]	PVR [mL]	LE	
Bach (2000) (6)	52	placebo	243	-5.5	n.s.	n.s.	1b	
		Cucurbita pepo (Prosta Fink <sup>1M</sup> forte)	233	-6.7 a	n.s.	n.s		
Darges et al. (1005)	24	placebo	100	-2.3	+1.1	-16.0	16	
(8)		Hypoxis rooperi (Harzol™)	100	-7.4 *	+5.2 *	-35.4 *		
Klippel et al. (1997)	26	placebo	89	-2.8	+4.3	-4.1	1b	
(9)		Hypoxis rooperi (Azuprostat™)	88	-8.2 °	+8.8 *	-37.5°		
Wilt et al. (2000) (7)	4-26	placebo Hypoxis rooperi	475	-4,9 b	+3.9 b	-28.6 b	1a	
Wilt et al. (2002) (10)	4-18	placebo Pygeum africanum (6-sitosterol)	1562	RR 2.07 b	+2.5 b	-13.2 b	1a	
Wilt et al. (2000) (11)	12-24	placebo Secale cereale (Cemilton <sup>1M</sup> )	444	RR 2.4 b	-1,8	-14.4	1a	
Wilt et al. (2002)	4-48	placebo	3139	-1.41 b	+1.86 b	-23 b	18	
(18)		Serenoa repens/ Sabal cerrulata						
Bont ot al. (2006)	62	placobo	112	0.7	0.01	10	16	
(19)		Serenoa repens	112	-0.7	+0.42	-14		
Carraro et al.	26	finasteride	545	-6.2	+3.2*	-	1b	
(1996) (20)		Serence repens (Permixon™)	553	-5.8	+2.7	-		
Debruyne et al.	52	tamsulosin	354	-4.4	+1.0	-	1b	
(2002) (21)		Serence repens (Permixon™)	350	-4.4	+1.8	-		
Schneider &	52	placebo	122	-4.7	+2.9	-4	1b	
Rübben (2004) (14)		Urtica dioica (Bazoton uno™)	124	-5.7 *	+3.0	-5		
Safarinojad (2005)	26	placebo	316	-1.5	+3.4	0	1b	
(15)		Urtica dioica	305	-8.0 *	+8.2 *	-37		
Lopatkin et al.	24	placebo	126	-4	+1.9		1b	
(2005) (16)		Sabal cerrulata + Urtica dioica (Prostatgutt™ forte)	127	-6 b	+1.8	-		
Sökeland &	48	finasteride	244	-5.6	+2.8	-17.1	1b	
Albrecht (1997) (17)		Sabal cerrulata + Urtica dioica (Prostatgutt™ forte)	245	-4.8	+2.0	-10.2		



Secale cereale



Urtica radix



Sabal serrulata



Cucurbita pepo

# **Plant Extracts**

- Phytotherapeutic agents are a heterogeneous group of plant extracts used to improve LUTS/BPH
- Problematic because of different concentrations of active ingredient(s) in different brands of the same phytotherapeutic agent
- Meta-analyses of extracts of the same plant are not justified and results of these analyses have to interpreted with caution
- Further studies are necessary to adequately judge plant extracts

3.4.6 Recommendations

The guidelines committee is unable to make specific recommendations about phytotherapy of male LUTS because of the heterogeneity of the products and the methodological problems associated with meta-

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12\_Male\_LUTS\_LR%20May%209th%202012.pdf]

Oelke<sup>©</sup>

# 'Emerging' Therapies

- Phosphodiesterase 5 (PDE5) inhibitors
  - Alone and in combination with  $\alpha$ -blockers
- · Available drugs include
  - Sildenafil

- Tadalafil

Vardenafil

Table 13: PDE5 inhibitors licensed in Europe for treating erectile dysfunction; key pharmacokinetic properties and doses used in clinical trials

Drugs	(hours)	(hours)	with male LUTS
Sildenafil	1 * (0.5-2)	3-5	1 x 25-100 mg
Tadalafil	2 (0.5-12)	17.5	1 x 2.5-20 mg
Vardenafil	1 * (0.5-2)	4-5	2 x 10 mg

No PDE5 inhibitor is indicated for use in LUTS and use is still

BUT tadalafil has been approved in Europe since October 2012

Oelke M et al. Management of Male LUTS. European Association of Urology. 2012 [www.uroweb.org/gls/pdf/12\_Male\_LUTS\_LR%20May%209th%202012.pdf]

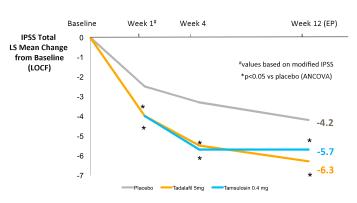
Oelke<sup>6</sup>

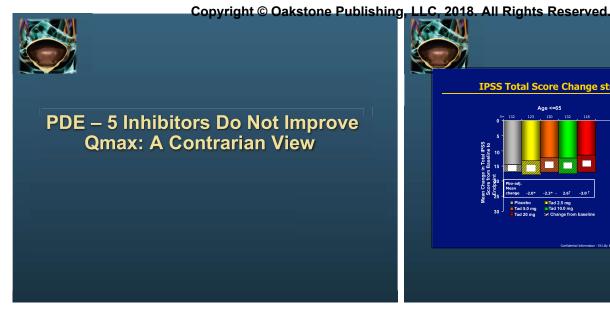
# **Efficacy PDE5 inhibitors**

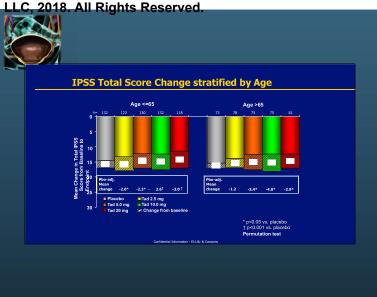
- In erectile dysfunction studies sildenafil reduces concomitant
- Short-term studies (<12 weeks)</li> have investigated PDE5 inhibitors in LUTS
- IPSS significantly and consistently reduced by 17-37%
- Bladder storage and voiding symptoms decrease
- Q<sub>max</sub> is increased dose-dependently
- Patient QoL is increased

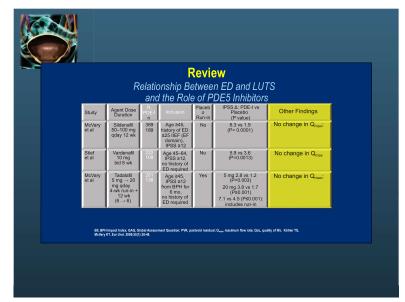
dalafii 1 x 10 mg/day -38.7 f Licuori et al 2009 [13] ‡ Oelke M et al. Management of Male LUTS. European Association of Urology [www.uroweb.org/gls/pdf/12\_Male\_LUTS\_LR%20May%209th%20201

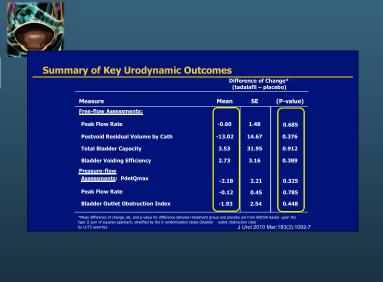
# **Both Tadalafil and Tamsulosin Improve IPSS ...**

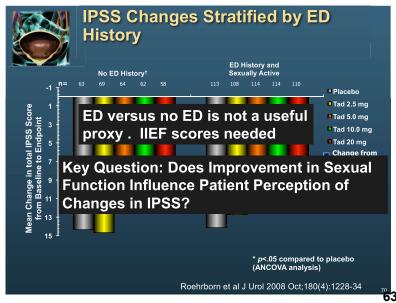


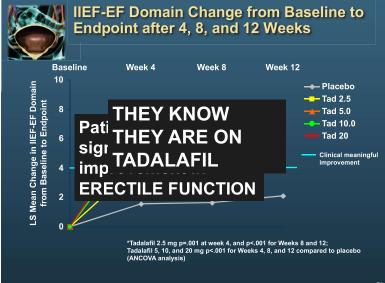












# **Primary and Secondary Outcomes**

Placebo Sildenafil (n=137) (n=129)

Men Who Claim They Have No Erectile Dysfunction Have Significant Improvement from a PDE – 5

Sexual Relationship 49.5 6.1±2.4 48.3 23.2±2.41

Therefore, Even Normal Men Were Unblinded: THEY KNEW THEY WERE TAKING TADAL FIL

\*N=138 in the placebo group for the IIEF-EF domain.

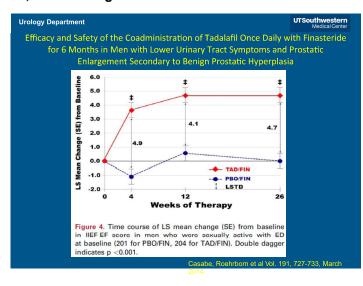
†P<0.0001 vs. placebo.

‡P=0.0112 vs. placebo.

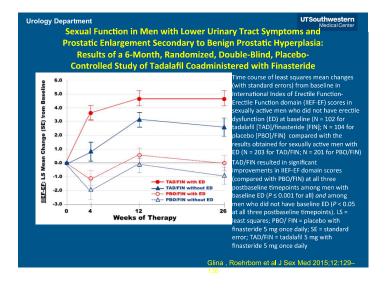
SEDITS data are end of treatment scores and included 138 men in the placebo group and 128 men in the sildenafil gro

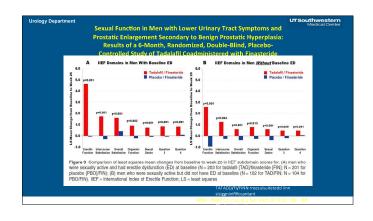
Shabsigh R. et al. Urology, 2010 Aug:76(2):373-9.

70



3/11/2017







# PDE – 5 Inhibitors / LUTS Thoughts

- Mechanism of Action is well defined for α<sub>1</sub> Adrenoceptor Antagonists
- No widely accepted mechanism of action for PDE – 5
  - Lots of theories
  - · ? bladder



# Which Agent?

# Lots of factors

- Specific findings assessed during evaluation
- Treatment preferences of the individual patient
- Ability of the treatment modality to change assessed findings



# Which Agent?

# What do patient and prescriber consider relevant?

- speed of onset
- efficacy
- side effects
- quality of life
- disease progression

elke M et al. Management of Male LUTS. European Association of Urology. 2



- Urologists have been playing small ball
- Need to expand
  - Advocacy
  - Preventive care
  - Holistic
- Expand beyond prostate and sexual function

# AUA Guidelines 2018: Lower Urinary Tract Symptoms Associated with Benign Prostatic Hyperplasia – Surgical Therapies

#### Lori Lerner, MD

Chief, Section of Urology Associate Professor of Urology VA Boston Healthcare System Boston University School of Medicine

#### **Disclosures**

- Lumenis, Inc Preceptor, prior consultant
- Boston Scientific Preceptor, prior consultant

All activities other than precepting HoLEP have been suspended during the duration of the Guidelines development/process

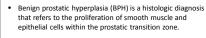
# **Learning Objective**



Be able to differentiate between non medical therapeutic options for BPH and understand which procedures are appropriate for which patients.

# **Background**







- While several hypotheses exist, BPH is likely the result of a multifactorial process, the exact etiology of which is unknown.

  The prevalence and the severity of lower urinary tract
- The prevalence and the severity of lower urinary tract symptoms (LUTS) in the aging male can be progressive and is an important diagnosis in the healthcare of patients and the welfare of society.

## **Purpose**

- The purpose of this revised guideline is to provide a useful reference on the effective evidence-based surgical management of male LUTS secondary to BPH (LUTS/BPH).
- The strategies recommended in this document were derived from evidence-base processes and a multi-disciplinary panel (general urology, surgical urology, primary care, patient advocacy).
- The most effective approach for a particular patient is best determined by shared decision making by the individual clinician and patient in the context of that patient's history, values, and goals for treatment.





# Methodology

- All modalities compared to TURP
- Whether or not this was best option is debatable, but guidelines should be taken within this context





**Evaluation and Preoperative Testing** 

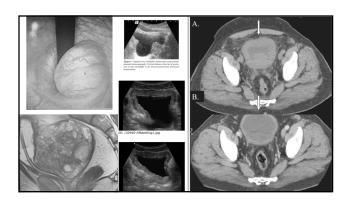
# **AUA-Symptom Index**

- 1. Clinicians should take a medical history and utilize the AUA-Symptom Index (AUA-SI) and urinalysis in the initial evaluation of patients presenting with bothersome LUTS possibly attributed to BPH; select patients may also require post-void residual (PVR), uroflowmetry, or pressure flow studies. (Clinical Principle)
  - AUA-SI is a validated self-administered questionnaire, can provide information regarding the symptom burden
  - Urinalysis can help to rule out other causes of LUTS
  - Shared decision making approach should be used to guide the need for further evaluation and possible treatment



### **Prostate Imaging**

- 2. Clinicians should consider assessment of prostate size and shape via abdominal or transrectal ultrasound, or cystoscopy, or by preexisting cross-sectional imaging (i.e. magnetic resonance imaging [MRI]/ computed tomography [CT]) prior to surgical intervention for LUTS attributed to BPH. (Clinical Principle)
  - Prostate size and morphology is important in the decision making process
- eg, Intravesical lobe and ball-valving middle lobe predict poor outcomes
   DRE and PSA are rough indicators of prostate size
- Reasonable to recommend imaging
- Abdominal or transrectal ultrasonography or cystoscopy
   Cross-sectional imaging using CT or MRI



## **PVR** Assessment

3. Clinicians should perform a PVR assessment prior to surgical intervention for LUTS attributed to BPH. (Clinical Principle)



- Multiple organizations include PVR measurement as part of the basic evaluation of LUTS
- Rising PVR can indicate medication failure and need for surgical intervention
- PVR does not seem to be a strong predictor of acute urinary retention - Clinically useful test that may drive management choices

### Uroflowmetry

- 4. Clinicians should consider uroflowmetry prior to surgical intervention for LUTS attributed to BPH. (Clinical Principle)
  - Generally accepted minimum threshold voided volume for adequate interpretation is 150 cc
    - Flow rate, shape of curve of voiding, duration
  - Underactive detrusor function
  - Bladder diverticulum



#### **Pressure Flow Studies**

5. Clinicians should consider pressure flow studies prior to surgical intervention for LUTS attributed to BPH when diagnostic uncertainty exists. (Expert Opinion)



- "Most complete" means to determine the presence of
- bladder outlet obstruction (BOO) with testing Likelihood of obstruction is greatly increased in patients with a Q<sub>max</sub> <10mL/s Large volume PVR weakly correlated with obstruction
- OAB symptoms and incontinence can be sequelae of obstruction or secondary to non-obstructive etiologies
- Surgery in these individuals may not lead to meaningful improvement

# **Surgical Therapy**



#### Surgery

6. Surgery is recommended for patients who have renal insufficiency secondary to BPH, refractory urinary retention secondary to BPH, recurrent urinary tract infections (UTIs), recurrent bladder stones or gross hematuria due to BPH, and/or with LUTS attributed to BPH refractory to and/or unwilling to use other therapies. (Clinical Principle)

- · Rates of surgical interventions dropping
- Those patients receiving surgery are generally older and have more medical comorbidities
- Surgery is mainstay in men with refractory urinary retention thought secondary to BPH

#### Bladder Diverticulum

7. Clinicians should not perform surgery solely for the presence of an asymptomatic bladder diverticulum; however, evaluation for the presence of BOO should be considered. (Clinical Principle)



- · Indications for surgical intervention: recurrent UTI, recurrent bladder stones, progressive bladder dysfunction, and renal insufficiency secondary to
- progressive bladder dysfunction
  Prior to surgery for bladder diverticulum, clinicians
  should perform assessment for BOO and treat as clinically indicated

# Transurethral Resection of the Prostate (TURP)

8. TURP should be offered as a treatment option for men with LUTS attributed to BPH. (Moderate Recommendation; Evidence Level: Grade B)

- TURP is gold standard
- TURP helps to reduce urinary symptoms associated with BPH:
- Frequent/urgent need to urinate
- Difficulty initiating urination Prolonged urination
- Nocturia
- Non-continuous urination
- Feeling of incomplete bladder emptying
- UTIs

#### Approach to TURP

9. Clinicians may use a monopolar or bipolar approach to TURP, depending on their expertise with these techniques. (Expert Opinion)

- No significant differences in efficacy or effectiveness between monopolar and bipolar approaches
- Safety differences:
- Bipolar TURP reduces
- Incidence of TUR syndrome
- ~ Catheterization time
- ~ Length of stay ~ Dilutional hyponatremia



### Simple Prostatectomy

- 10. Clinicians should consider open, laparoscopic or robotic assisted prostatectomy, depending on their expertise with these techniques, for patients with large prostates. (Moderate Recommendation; Evidence . Level: Grade C)
- Complications increase with increasing resection time and increasing resected tissue volume following monopolar TURP
- Bipolar TURP extends safe duration of TURP and use for larger glands
- Open simple prostatectomy (OSP) compared to TURP
   OSP: Greater maximum flow rate at 12 months
- Lower reoperation - No difference in blood transfusion needs

### Transurethral Incision of the Prostate (TUIP)

- 11. TUIP should be offered as an option for patients with prostates ≤30g for the surgical treatment of LUTS attributed to BPH. (Moderate Recommendation; Evidence Level: Grade B)
- Used to treat small prostates (usually defined as ≤30g)
- · TUIP has lower rate of retrograde ejaculation, need for blood transfusion, compared to TURP
- · Procedure can be performed with "hot knife" or laser
- ED in 8% with TUIP, 20% with TURP



I. Abd-El Kader O. et al. Afr J Urol 2012: 18: 29

### Transurethral Vaporization of the Prostate (TUVP)

- 12. Bipolar TUVP may be offered to patients for the treatment of LUTS attributed to BPH. (Conditional Recommendation; Evidence Level:
- Multiple electrode types
  Metanalysis outcomes were similar in both groups

   Long-term response to treatment based on varying
  definitions using the International Prostate Symptom
  Score (IPSS)

   Mean change in IPSS through 7 years

   Need for reoperation

   Litinary incontinence
- Urinary incontinence
- However, need for blood transfusion was lower for TUVP compared with

### Photoselective Vaporization of the Prostate (PVP)

- 13. Clinicians should consider PVP as an option using 120W or 180W platforms for patients for the treatment of LUTS attributed to BPH. (Moderate Recommendation; Evidence Level: Grade B)
- Generally similar outcomes with regards to symptomatic, urinary improvement in LUTS/BPH and complication rates between TURP and PVP Need continuous irrigation due to high temperatures that may develop
- PVP may be more efficacious for smaller volume prostates Increased probability of intraoperative conversion to TURP for prostate volumes > 60 cc to 80 cc
- Other laser technologies are either investigational or had results that were not considered sufficient or safe to recommend them for routine use

### Prostatic Urethral Lift (PUL)

14. Clinicians should consider PUL as an option for patients with LUTS attributed to BPH provided prostate volume <80g and verified absence of an obstructive middle lobe; however, patients should be informed that symptom reduction and flow rate improvement is less significant compared to TURP. (Moderate Recommendation; Evidence Level: Grade C)

- Response and safety favors TURP vs PUL
- IPSS goal reached
- 91% with TURP 73% with PUL
- Relative risk = 2.7 for serious and non-serious treatment-related harms
- Incontinence favors PUL vs TURP
- 1.7% vs 17.1%



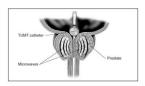
### PUL Preservation of Sexual Function

- 15. PUL may be offered to eligible patients concerned with erectile and ejaculatory function for the treatment of with LUTS attributed to BPH. (Conditional Recommendation; Evidence Level: Grade C)
  - Sexual function of men with normal or moderate ED at baseline was unaffected, and those with severe ED reported modest improvement



### Transurethral Microwave Therapy (TUMT)

16. TUMT may be offered to patients with LUTS attributed to BPH; however, patients should be informed that surgical retreatment rates are higher compared to TURP. (Conditional Recommendation; Evidence Level: Grade C)



### Water Vapor Thermal Therapy

17. Water vapor thermal therapy may be offered to patients with LUTS attributed to BPH provided prostate volume <80g; however, patients should be informed that evidence of efficacy, including longer-term retreatment rates, remains limited. (Conditional Recommendation; Evidence Level: Grade C)



- Improvement in I-PSS was 74% with water vapor thermal therapy vs 31% with sham
- Serious AEs were similar between therapy and
- sham groups

   Incidence of non-serious transient adverse events was significantly higher in the water vapor thermal therapy group (dysuria, hematuria, frequency and urgency, and UTI)

### Water Vapor Thermal Therapy and Sexual Function

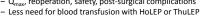
- 18. Water vapor thermal therapy may be offered to eligible patients who desire preservation of erectile and ejaculatory function. (Conditional Recommendation; Evidence Level: Grade C)
  - Short term: few harms occurred in the water vapor thermal therapy group between months 3 and 12
  - 2% experienced a decrease in ejaculatory volume
  - Long-term:
    - No de novo ED was reported
  - No significant changes in IIEF-EF scores or ejaculatory functions
  - Bother associated with ejaculation was assessed was significantly improved at 12 and 24 months following treatment

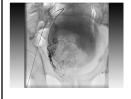
### Transurethral Needle Ablation (TUNA)

- 19. TUNA is not recommended for the treatment of LUTS attributed to BPH. (Expert Opinion)
- TUNA reduces prostatic volume less than initially anticipated
- BPH histologic architecture is likely replaced in part with scar
- Lack of peer-reviewed publications
- Decreasing clinical relevance
- · Attempts to identify favorable candidates for TUNA have been unsuccessful

### Laser Enucleation

- 20. Clinicians should consider holmium laser enucleation of the prostate (HoLEP) or thulium laser enucleation of the prostate (ThuLEP), depending on their expertise with either technique, as prostate size-independent suitable options for the treatment of LUTS attributed to BPH. (Moderate Recommendation; Evidence Level: Grade B)
  - · Superficial penetration, excellent coagulative properties
  - Outcomes measures generally similar to TURP
  - Q<sub>max</sub>, reoperation, safety, post-surgical complications





### Prostate Artery Embolization (PAE)

- 21. PAE is not recommended for the treatment of LUTS attributed to BPH outside the context of a clinical trial. (Expert Opinion)
  - Newer, largely untested MIST for BPH
  - · Available trial results present conflicting picture, relative to TURP
    - Small trials
  - No difference in outcomes, or TURP superiority.

Medically Complicated Patients

### Patients Receiving Anti-Coagulant Therapy

22. HoLEP, PVP, and ThuLEP should be considered in patients who are at higher risk of bleeding, such as those on anti-coagulation drugs. (Expert Opinion)

- Need for a blood transfusion (either peri- or post-operatively) was significantly less likely with HoLEP and ThuLEP, as compared to TURP
- Superficial penetration, shallow coagulation zones
- PVP is safe and effective for patients who continue their anticoagulant/antiplatelet therapy





### **Future Directions**

Disease Etiology

No good animal models available

Management of Nocturia

 unique symptom complex requiring special concern and judicious evaluation

Urodynamic Evaluation and Imaging

**New Therapeutic Options** 

Many new, promising options

Treatment Failure

Treatment Comparative Efficacy

### **Prostate Cancer Screening**

Kristen R. Scarpato, MD MPH August 8, 2018 • I have no disclosures

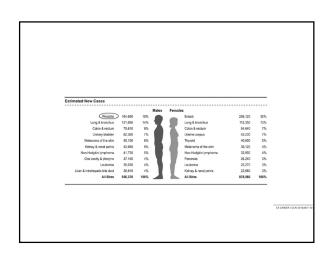
### Objectives

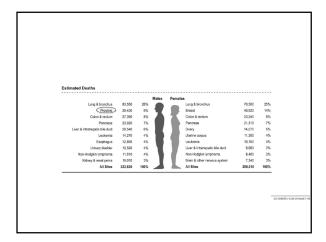
- At the conclusion of this presentation the participant should be able to:
  - Describe goals of screening
  - Understand the history of PSA as a screening tool
  - Be familiar with non-PSA screening tools
  - Describe current recommendations for prostate cancer screening

### Outline

- Prostate cancer statistics
- General screening principles
- PSA Screening
- Impact of decreased PSA screening
- Non-PSA Screening tools
- Current recommendations AUA, NCCN, USPSTF

### **PROSTATE CANCER STATISTICS**





### **SCREENING**

### What is A Good Screening Test?

- Sensitive
- Specific
- Non-invasive and safe
- Detects a common condition
- Detects a harmful condition
- Detects a condition that has an effective treatment, which works better in the pre-clinical phase than after the condition is clinically detected
- Cost-effective
- Benefits outweigh harms

Adapted from James McKiernan of Columbia University

### What is PSA?

- Glycoprotein produced by epithelial cells of prostate gland
- Normally low levels in serum
- Trauma, infection, inflammation, malignancy results in a larger amount of PSA in serum
- Therefore, serves as a marker for prostate disease
- (PSA is not a cancer-specific marker)

### **PSA Screening**

- PSA correlates with risk of prostate cancer
- The Prostate Cancer Prevention Trial (PCPT) found that normal DRE and...
  - PSA ≤4.0  $\rightarrow$  15% had prostate cancer
  - PSA 4-10 → 30 35% had prostate cancer
  - PSA >10 → > 67% likelihood of prostate cancer.

### **PSA Screening**

- Early PSA era → screen all, treat all
- Current → limit screening, limit treatment
- Controversial!

### **PSA Screening**

### Benefits

### Reduces risk of dying from prostate cancer

### Harms

- Overdiagnosis
- Overtreatment
- Increased cost

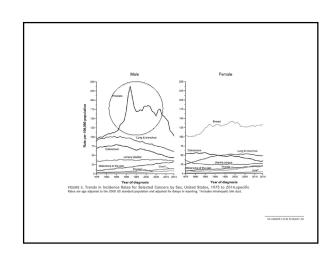
### Is PSA a Good Screening Test?

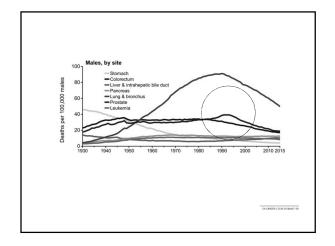
- Sensitivity at 4.0 ng/ml = 75%
- Specificity at 4.0 ng/ml = 25%
- Non-invasive and safe yes
- Detects a common condition yes
- Detects a harmful condition yes (but also indolent ca)
- Detects a condition that has an effective treatment, which works better in the pre-clinical phase than after the condition is clinically detected yes (but debated)
- Cost-effective debated
- Benefits outweigh harms debated

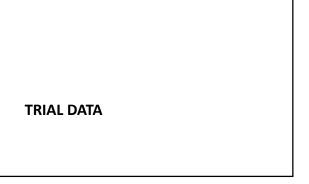
Adapted from James McKiernan of Columbia University

### Relationship to Incidence

- Cancer incidence impacted by:
  - Risk factors (age, race, family history)
  - behaviors associated with risk
  - Medical practice →Screening
- This is particularly relevant in prostate cancer where screening practices have changes based on USPSTF recommendations







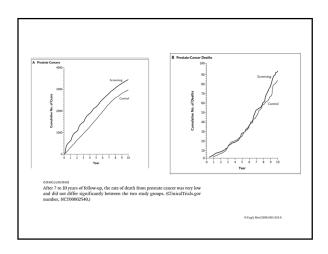
### Randomized Screening Trials

- PLCO no difference in prostate cancer specific mortality with yearly PSA screening
- ERSPC significant survival benefit from regular PSA screening
- CAP no difference in mortality with a single PSA screen

## Mortality Results from a Randomized Prostate-Cancer Screening Trial

- First report from the PLCO The US-based randomized screening trial
- 76,693 men aged 55-74
- Routine screening → annual PSA and DRE
- Usual care → control group, patients could elect to screen
- No reduction in PCa-specific mortality associated with screening
- Median follow-up of 10 years

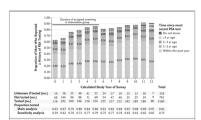
N Engl I Med 2009:360:1310-9



# Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO)

- · Significant flaws
- Prescreening with PSA in > 40% of the study subjects
- Contamination (by PSA testing) in 70% of the "unscreened" control cohort

### Reevaluating PSA Testing Rates in the PLCO Trial

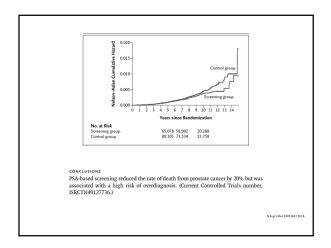


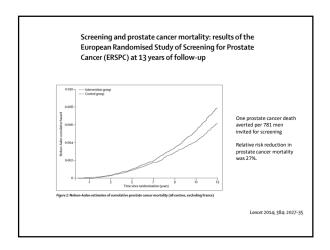
N ENGL J MED 374;18 NEJM.ORG MAY 5, 2016

Screening and Prostate-Cancer Mortality in a Randomized European Study

- The European-based randomized screening trial (ERSPC)
- 182,000 men aged 50-74
- Screening arm PSA every 4 years
- Control arm No PSA screening
- Reported statistically significant reduction in relative risk of death from prostate cancer and decreased risk of developing metastatic disease in screening group

N Engl J Med 2009;360:1320





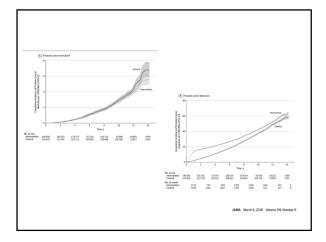
# European Randomized Study of Screening for Prostate Cancer (ERSPC)

- Some criticism...
- 30% of control group underwent PSA screening
  - Contamination
  - Lower than PLCO
- Variable screening protocols
- Differences in PCa treatment

Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality
The CAP Randomized Clinical Trial

- 1º objective: to evaluate the effect of a single PSA screen and standard work up on PCSM
  - 2°: stage, grade, all-cause mortality
- Cluster RCT
  - 419,582 men, 2001 2009
  - -50 69 yrs (59)
- Invited to attend a single PSA testing clinic vs unscreened practice
- Median follow up 10 years

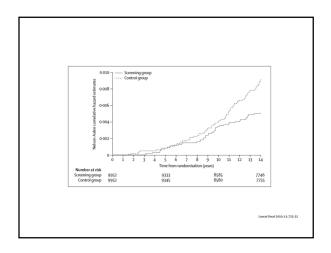
JAMA March 6, 2018 Volume 319, Number



### **Goteborg Trial**

- PSA screening trial, randomized
- 20,000 men age 50 64
  - Screening: PSA every 2 years
  - Control: No PSA testing
- Medial follow up 14 years
- Screening significantly reduced the relative risk of death from prostate cancer and decreased risk of being diagnosed with metastases

Lancet Oncol 2010; 11: 725-



### Goteborg Study – follow up

- 18 year follow up
- Screened 1369 cases, 79 PCa deaths
- Control 962 cases, 122 PCa deaths
- Findings: organized screening was associated with an absolute PCa specific mortality reduction of 0.72% and relative risk reduction of 42%

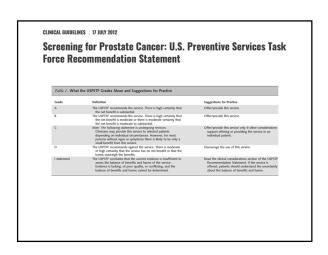
EUROPEAN UROLOGY 68 (2015) 354-360

# Goteborg Trial Observed and expected mortality of proteins cancer in the Obtology protein cancer screening group Central gro

### **USPSTF RECOMMENDATIONS**

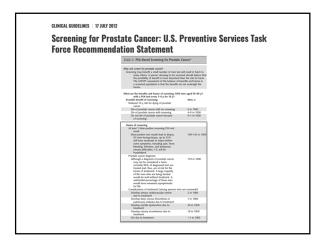
### **USPSTF** Recommendations

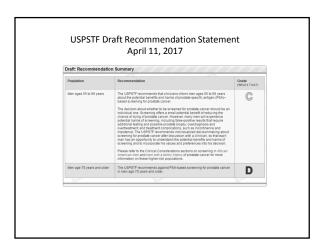
- 2008: recommended against routine use of PSA testing (Grade D) in men ages 75 and older
- 2012: recommended against routine use of PSA testing (Grade D) in all men due to growing concerns regarding overdiagnosis and overtreatment.
- April 2017: issued a draft statement revising its recommendation for men aged 55-69 years to informed decision making (Grade C)

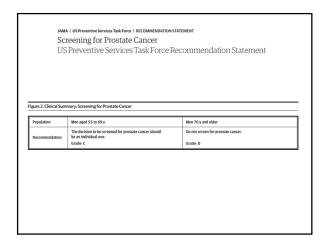


### **USPSTF** Recommendations

- Evaluated available evidence in 2011 (PLCO and ERSPC)
- Reduction in prostate cancer deaths from PSA screening is at most very small
- Furthermore, significant harm from screening weighed against indolent nature of most cancer







IMPACT OF DECREASED PSA SCREENING

Trends in United States Prostate Cancer Incidence Rates by Age and Stage, 1995–2012

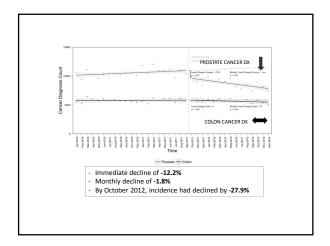
- SEER analysis through 2012 →slight increase in metastatic disease in men 50-69 y/o
- Declining localized/ regional prostate cancer incidence rates; however, incidence rates of distant-stage disease are now increasing in younger men.
- Impact: This trend may adversely affect prostate cancer mortality rates.

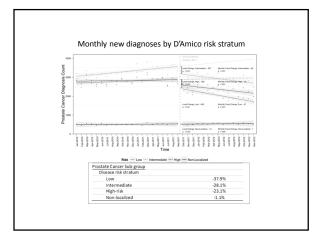
Cancer Epidemiol Biomarkers Prev; 25(2) February 201

Effect of the USPSTF Grade D Recommendation against Screening for Prostate Cancer on Incident Prostate Cancer Diagnoses in the United States

- National Cancer Database through 2012
- Evaluated rate of new diagnoses in the US before and after publication of the USPSTF draft recommendations
- Over 350,000 cases from 1,350 hospitals

Vol. 194, 1587-1593, December 2015





Effect of the USPSTF Grade D Recommendation against Screening for Prostate Cancer on Incident Prostate Cancer Diagnoses in the United States

- Potential benefits of USPSTF policy
  - Decreased harms of diagnosis and treatment
    - Low risk disease
    - Elderly and infirm
- Potential harms of USPSTF policy
  - Missed opportunities to diagnose and treat
    - Intermediate and high-risk disease
    - Young and healthy
    - Effect on high-risk and vulnerable populations

Vol. 194, 1587-1593, December 2015

### Recent Changes in Prostate Cancer Screening Practices and Epidemiology

- · Review of 26 studies on effect of USPSTF
- 2012-2016
- Decrease in PSA testing, prostate biopsy
- Decline in incidence of localized prostate cancer, all risk categories
- Shift towards higher burden of disease at presentation – concern for reverse stage migration

Vol. 198, 1230-1240, December 2017

### **OTHER SCREENING TOOLS**

### **Digital Rectal Exam**



### Digital Rectal Exam

- Consider as a baseline tool; complementary
- May detect some clinically significant cancers in patients with normal PSA
- Abnormal DRE increases probability of cancer detection and high grade disease (PCPT, PLCO)
- Should not be used as a stand-alone test
- Low PPV in men with a normal PSA

### Biopsy

- Biopsy also a screening tool
- Saturation, transperineal, fusion
- Negative but PSA continues to elevate?
  - Consider multiparametric MRI
- If MRI-visible lesions are present?
  - Consider fusion biopsy
  - The associated prostate cancer risk with a positive mpMRI result is 34-68%

### **Biomarkers**

- Focus on limiting overdiagnosis; improve specificity
- Not yet recommended as first line screening tests
- May be useful if
  - No prior biopsy (%free, PHI, 4K)
  - Prior negative biopsy (PCA3, mpMRI)

### Percent-free PSA (%f PSA)

- Majority of PSA circulated bound to proteins
   Unbound form of PSA, "free"
- FDA approved early detection for PSA 4 10
- Significantly lower in men with cancer
- 25% fPSA cutoff detects 95% of prostate cancers while avoiding 20% of unnecessary biopsies

### Prostate Health Index (PHI)

- tPSA, fPSA, proPSA
- FDA approved 2012 (PSA 4 10)
- Increased sensitivity of prostate cancer detection, discriminates high vs. low grade
- · Informs decision to biopsy
- Been shown to decrease biopsy procedures

### 4Kscore

- tPSA, fPSA, nK2, intact PSA
- Age, DRE, prior biopsy
- Provides estimate of probability of high-grade cancer on biopsy
- High AUC (0.82)
- Informs decision to biopsy
- 65% reduction in prostate biopsies (Konety et al, 2015)

### 4K score

- · Prospective trial
- 1° outcome: diagnosis ≥ 7 prostate cancer
- 1,012 men scheduled for bx at 26 US Centers
   Oct 2013 April 2014
- 231 (23%) diagnosed with Gleason ≥ 7
- Outperformed PCPT (AUC: 0.82 vs 0.74)
- Avoid 30-58% biopsies
- Delayed dx of 1–4% Gleason ≥7

Parekh et al. Eur Urol 2015

### PCA3

- Prostate specific RNA
- Over-expressed in prostate cancer
- Use post DRE urine specimen
- Identify clinically significant PCa
- Data supports use to inform repeat biopsy decision making
  - FDA approved for re-biopsy

### **Prostate MRI**

- In men undergoing initial biopsy...
- MRI guided / ultrasound fusion may increase detection of clinically significant cancers
- Lower detection of lower-risk cancers

PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2

- International collaboration
- "Promote global standardization and diminish variation in the acquisition, interpretation and reporting" of prostate mpMRI
- Categories that summarize levels of suspicion or risk of clinically significant prostate cancer
- Assist in selection of patients for biopsies and management

(UEOPEAN UROLOGY 69 (2016) 16-4

PI-RADS Prostate Imaging – Reporting and Data System: 2015, Version 2

- Score 1 = highly unlikely (very low)
- Score 2 = unlikely (low)
- Score 3 = equivocal (intermediate)
- Score 4 = likely (high)
- Score 5 = highly likely (very high)

...... to have clinically significant PCa

EUROPEAN UROLOGY 69 (2016) 16-4

AUA Policy Statement on the Use of Multiparametric Magnetic Resonance Imaging in the Diagnosis, Staging and Management of Prostate Cancer

- Summary of available data re: effectiveness in diagnosis and management
- Provide practical recommendations: screening, diagnosis, staging, surveillance
- Expert review of available + expert consensus in absence of data

J Linst, 2017 Oct; 198(4):832-8

AUA Policy Statement on the Use of Multiparametric Magnetic Resonance Imaging in the Diagnosis, Staging and Management of Prostate Cancer

### **SCREENING**

- NO evidence support the use of mpMRI for routine screening
- Insufficient data for routine use as initial evaluation in biopsy-naïve patients
- Evidence for mpMRI for patients with previous negative biopsy and persistent concern for PCa

111ml 2017 On 18801 833 8

### Other biomarkers

- SelectMDx
- ConfirmMDx
- The Mi-Prostate Score (MiPS)
- ExoDx Prostate (IntelliScore)

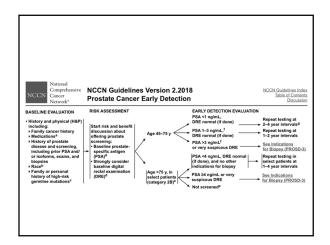
### **GUIDELINES**

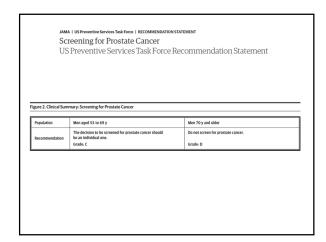
### Early Detection of Prostate Cancer: AUA Guideline (2013)

- PSA screening in men <40 years is not recommended</li>
- Routine screening in men between the ages of 40
   54 years at average risk is not recommended
- For men ages 55 69, the decision to undergo PSA screening involves shared decision making
  - Screening interval of two years or more
- Routine screening in men >70 or in any man with <10-15 year life expectancy is not recommended</li>

# Early Detection of Prostate Cancer: AUA Guideline (2013)

 Intended to be used by urologists as a means of detecting prostate cancer in early, presymptomatic men





### **CONCLUSIONS**

### Smarter Screening

- Know the facts
- Healthy men / life expectancy
  - Most likely to benefit
- Shared decision making
- Longer screening intervals
- Utilize additional testing when appropriate

### Conclusions

 PSA screening remains controversial but decreases risk of death from prostate cancer

### Thank You



### **Disclosures**

• Research Grants: NCI, PCF

Consulting Fees: Lilly

• Conference Travel Expenses: Sanofi

### Outline

- · Rationale and utilization trends
- Barriers to uptake of active surveillance
- Outcomes of active surveillance

### **Overdiagnosis and Overtreatment of Prostate Cancer**

Stacy Loeb  $^{a,\,c}$ , Marc A. Bjurlin  $^a$ , Joseph Nicholson  $^b$ , Teuvo L. Tammela  $^c$ , David F. Penson  $^d$ , H. Ballentine Carter  $^c$ , Peter Carroll  $^f$ , Ruth Etzioni  $^x$ 

- •Up to 67% cases overdiagnosed depending on the population and criteria
- •Historically the vast majority of low-risk patients received radical treatment
  - •Overtreatment → unnecessary side effects

### Reviews BJUI BJU International

The Melbourne Consensus Statement on the early detection of prostate cancer

Declan G. Murphy<sup>1,23</sup>, Thomas Ahlering<sup>4</sup>, William J. Catalona<sup>4</sup>, Helen Crowe<sup>2,3</sup>, Jane Crowe<sup>3</sup>, Noel Clarke<sup>19</sup>, Matthew Cooperberg<sup>4</sup>, David Gillath<sup>11</sup>, Martin Gleave<sup>12</sup>, Stacy Loeb<sup>2</sup>, Monique Roobol<sup>14</sup>, Oliver Sartor<sup>1</sup>, Tom Pickles<sup>13</sup>, Addie Wootten<sup>3</sup>, Patrick C. Walsh<sup>2</sup> and Anthony J. Costellic<sup>2,2</sup>

 Consensus Statement 2: "Prostate cancer diagnosis must be uncoupled from prostate cancer intervention"

# 2012 US Preventive Services Task Force (USPSTF) Guidelines

- Grade D recommendation against PSA
  - -Per 1000 men screened:
    - 1 fewer prostate cancer death
    - 30-40 men with incontinence or erectile dysfunction due to treatment
    - 2 men with serious cardiovascular events
    - 1 venous thrombosis

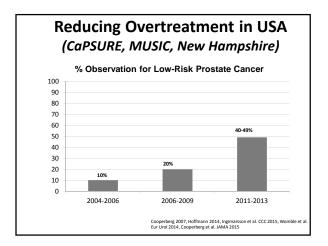
www.uspreventativeservicestaskforce.org

2018 US	PSTF Recommendation	ons
Population	Recommendation	Grade
Age 55-69	Recommends that clinicians inform men about the potential benefits and harms of screening	С
Age ≥70	Recommends against PSA-based screening	D

# Active Surveillance Factored Into Changes in Screening Guidelines

This recommendation replaces the 2012 USPSTF recommendation<sup>31</sup> on PSA-based screening for prostate cancer. In 2012, the USPSTF concluded that, although these are potential benefits of screening for prostate cancer, these benefits do not outweigh the expected harms of the concluded that, although these are potential benefits of screening for prostate cancer, these benefits do not outweigh the expected harms of the concluded that the sense of the Concluded that the conclusion is not for contract cancer and risk of metabactic obsease. Longer-ferm follow-up of the ERSPC trial shaft from some ERSPC trial shaft brial should be subset of ERSPC trial shaft concluded that the conclusion is not screening for prostate cancer prevents a concerning 100 man aged 55 to 50 years may prevent approximately 3 men from developing in instability prostate cancer. Longer-ferm year results. Studies continue to demonstrate the harms of EAA-based screening, including false-poster exists, complications from transrectal prostate biopies, overdiagnosis (which may occur in 2016-56) of cases of screen-detected cancer, based on estimates from transrectal prostate biopies, overdiagnosis (which may occur in 2016-56) of cases of screen-detected cancer, based on estimates from transrectal prostate biopies, overdiagnosis (which may occur in 2016-56) of cases of screen-detected cancer, based on estimates from transrectal prostate biopies, overdiagnosis (which may occur in 2016-56) of cases of screen-detected cancer, based on estimates from transrectal prostate biopies, overdiagnosis (which may occur in 2016-56) of cases of screen-detected cancer, based on estimates from transrectal prostate biopies, overdiagnosis (which may occur in 2016-56) of cases of screen-detected cancer, based on estimates from transrectal prostate biopies, overdiagnosis (which may occur in 2016-56) of cases of screen-detected cancer, based on estimates from transrectal prostate cancer and provincion. The ERSINGER results of the detected of the commendation of men aged 55 to

"The change in recommendation grade further reflects new evidence about and increased use of active surveillance of lowrisk prostate cancer, which may reduce the risk of subsequent harms from screening."

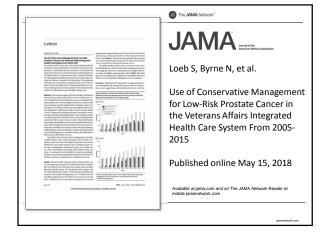


The Association Between Evaluation at Academic Centers and the Likelihood of Expectant Management in Low-risk Prostate Cancer

Nataniel H. Lester-Coll, Henry S. Park, Charles E. Rutter, Christopher D. Corso, Brandon R. Mancini, Debra N. Yeboa, Simon P. Kim, Cary P. Gross, and James B. Yu

- National Cancer Database (2010-2013)
  - 70% newly diagnosed cases in USA
  - N=91,556 low risk
- Expectant management use
  - 17% academic centers vs. 8% community centers
  - Multivariable analysis: 2.7x greater at academic centers

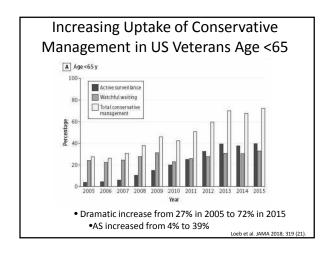
Lester Coll et al. Urology 2016

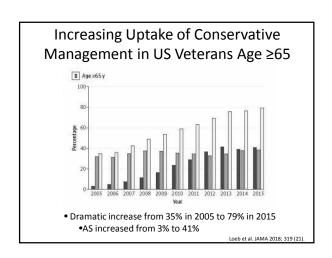


### Methods

- From 2005-2015, n=125,083 US veterans diagnosed with low-risk PCa (PSA<10, Gleason ≤6, cT1/T2a)
- Sub-classification of AS vs. watchful waiting using codes
  - AS if ≥2 PSA and 1 biopsy within 2 years after diagnosis, otherwise classified as WW
- · Statistical analysis:
  - Cochrane-Armitage test used to examine trends in conservative management use over time, stratified by age
  - Multivariable logistic regression used to identify predictors of conservative management vs. treatment, and AS vs. WW

Loeb et al. JAMA 2018; 319 (21).

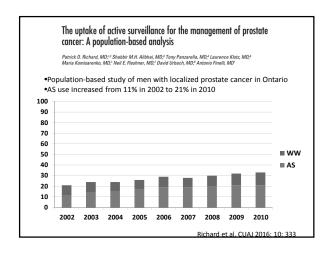


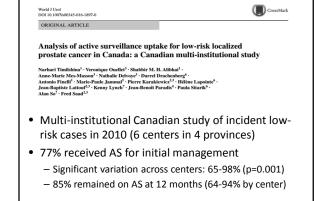


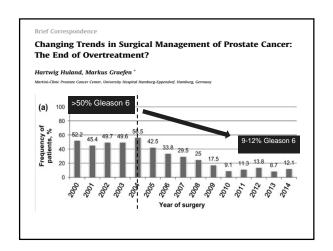
# Conservative Management in VA: Conclusion

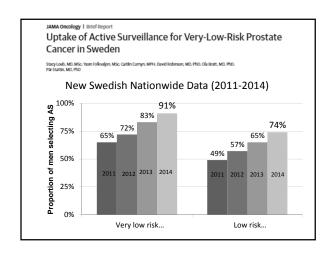
- Conservative management uptake has increased significantly in a nationwide sample of U.S. veterans with low-risk prostate cancer
- These results suggest a substantial reduction in overtreatment during the past decade, and compare favorably with prior U.S. studies in different healthcare settings

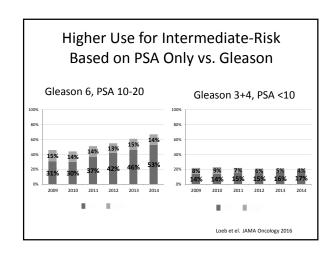
Loeb et al. JAMA 2018; 319 (21).











### **Active Surveillance Guidelines**

### JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Active Surveillance for the Management of Localized Prostate Cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

- <u>Recommended management</u> for most low-risk patients (Gleason ≤6)
- May be offered to select patients with low-volume, intermediate-risk PCa (Gleason 3+4=7)
- Watchful waiting more appropriate if <5 year life expectancy</li>

Chen et al. JCO 2016 epub.

# 2017 AUA/ASTRO/SUO Guideline: Clinically Localized Prostate Cancer

### Very Low Risk

 Clinicians should recommend active surveillance as the best available care option (Strong Recommendation; Evidence Level A)

### Low Risk

- Clinicians should recommend active surveillance as the preferable care option (Moderate Recommendation; Evidence Level B)
- Clinicians may offer definitive treatment (i.e. radical prostatectomy or radiotherapy) to select patients who may have a high probability of progression (Conditional Recommendation; Evidence Level B)

### Intermediate Risk

 Active surveillance may be offered to select patients with <u>favorable</u> intermediaterisk localized prostate cancer; however, patients should be informed that this comes with a higher risk of developing metastases compared to definitive treatment (Conditional Recommendations, Evidence Level C)

### 2018 National Comprehensive Cancer Network Guidelines

- · Very low-risk
  - Observation if life expectancy <10y
  - AS if life expectancy 10-20y
  - AS/RT/RP if life expectancy ≥20y
- Low-Risk and Favorable intermediate-risk:
  - Observation if life expectancy <10y</p>
  - AS/RT/RP if life expectancy ≥10y

### 2018 European Association of Urology **Position Statement**

- Include all men with low-risk PCa
  - Men with life expectancy >20 yr should be properly counseled about the lack of very long-term data of AS
- Low-volume GG2: Increased risk of progression and metastasis
  - Informed consent about lack of robust data
- Consider central pathological review of biopsy specimens when commencing long-term conservative management

### Outline

- · Rationale and utilization trends
- Barriers to uptake of active surveillance
- · Outcomes of active surveillance

### Challenge 1:

Barriers to Uptake -Patients -Physicians

### Increasing Patient Acceptance of AS-Renaming "Gleason 6" Disease

- "Cancer" is an emotion-laden term but Gleason 6 has limited metastatic potential
  - Proposals to remove "cancer" label- NOT adopted
- New grade groups adopted reclassifying 6-10 as 1-5

Traditional Gleason score	Grade group
6	1
3+4=7	2
4+3=7	3
8	4
9-10	5

Epstein et al. Eur Urol 2016 epub



the New Grade Groups: Initial Qualitative Study

Stacy Loeb a,b,c,\*, Caitlin Curnyn b, Erica Sedlander

• 80% of patients feel more comfortable with active surveillance for "grade group 1" vs "Gleason 6"

Barriers to AS Uptake: Biopsy Risks

- Low and favorable intermediate-risk CaP in SEER-Medicare data (2009-2011)
- Significantly lower uptake of AS in men with complications on diagnostic biopsy

Adamsky et al. AUA 2017

### **BJUI**

Qualitative study on decision-making by prostate cancer physicians during active surveillance

Stacy Loeb\*,  $^{\uparrow, \uparrow, \$}$ , Caitlin Curnyn $^{\uparrow}$ , Angela Fagerlin $^{\eta, *}$ \*, Ronald Scott Braithwaite $^{\uparrow}$ , Mark D. Schwartz $^{\uparrow, \$}$ , Herbert Lepor\*- $^{\uparrow, \$}$ , Herbert Ballentine Carter $^{\uparrow \uparrow}$  and Erica Sedlander $^{\uparrow}$ 

- In-depth interviews with US prostate cancer providers until thematic saturation was reached (n=24)
- Transcripts were independently coded by 2 researchers
- Matrix analysis and NVivo software used for organization and further analysis

### Increasing Acceptance of AS-Qualitative data on Challenges for US Providers

- Varying experience/exposure to AS during training
  - "We train people to do something. We are by nature doers and AS is not really part of what a surgeon is wired to do."
- Concerns about inflicting "harm" and legal risk
  - "It's possible that you miss the window of curability on your watch. They could be hurt by that choice. That's a lot of responsibility."
  - "There's obviously some degree of liability."
- Financial incentives
  - "In Europe where there is no fee for service system the uptake of AS is exponentially higher than it is in the U.S."

Loeb et al. BJUI 2016 epub.

### Challenge 2:

# Risk of upfront misclassification

### **Optimizing Patient Selection**

- PSA, clinical stage and standard biopsy result in substantial rates of misclassification (>1/3)
- Substantial biologic heterogeneity within broad risk groups
- Role for imaging and biomarkers to refine selection

Shapiro & Johnstone Urology 2012; 80: 661. Loeb et al. Eur Urol 2013 epub. Lee et al. Can J Urol 2010; 17: 5429 Ross et al. JCO

### Genomic Tests for Risk Stratification

	Company	Reported Endpoints	Technique	Sample
Oncotype DX	Genomic Health	Adverse pathology (+Mets, PCa death)	RT-PCR	Highest grade tumor
Prolaris	Myriad	PCa death (+Mets w Tx)	RT-PCR	Largest tumor
Decipher	GenomeDx	Metastasis (+High grade, PCa death)	Microarray	Highest grade tumor

### **Genomic Testing**

AUA Guidelines (2017)

Among most low-risk localized prostate cancer patients, tissue based genomic biomarkers have not shown a clear role in the selection of candidates for active surveillance. (Expert Opinion)

NCCN(2018)

Men with low or fluvorable intermediate risk diseases may consider the use of the following tumor-based molecular assays: Decipher, Oncope DX Prostate, Proteins Promark, Retrospective studies have shown that milecular assays performed on prostate biopsy or reliad prostate/corrup seriorisms provide prosposic information independent of NCON risk groups. These include, but are not limited to, likelihood of death with conservative management, likelihood of biochemical progression a radical prostateomy or external beam through, and likelihood of developing metastasis after radical prostateomy or external beam through, and likelihood of developing metastasis after radical prostateomy or external beam through and likelihood of developing metastasis after radical prostateomy or external beam radio progression as



- No evidence on clinical outcomes of patients whose treatment was informed by Prolaris
- Economic evaluation for publicly funding Prolaris
  - Net budget impact= \$41.3M in 5y (mostly from cost of the
  - \$7.3 million estimated savings by increasing AS insufficient to offset high
- Patients viewed the test as potentially helpful but were unsure it would ultimately change their treatment

### Predictors of Reclassification and/or Metastatic Disease During AS

- Patient factors
  - African American
  - Obesity
- Risk classification (Intermediate > Low > Very low)
  - PSA density >0.15
  - Greater extent of cancer on biopsy
  - Gleason ≥3+4=7 (>3x greater risk of metastasis)

Loeb et al. Eur Urol 2015; 67: 619. Yamamoto et al J Urol 2016; 195: 1409.

### Challenge 3:

### **Monitoring Protocols**

### Monitoring During AS- NCCN



NCCN Guidelines Version 3.2018 **Prostate Cancer** 

Active surveillance<sup>r</sup>

PSA no more often than every 6 mo unless clinically indicated

DRE no more often than every 12 mo unless clinically indicated

Repeat prostate biopsy no more often than every 12 mo unless clinically indicated

Consider mpMRI if anterior and/or aggressive cancer is suspected when PSA increases and systematic prostate biopsies are negative

### Monitoring During AS- EAU 2018

- PSA at least once every 6 months
- DRE at least once a year
- Repeated biopsy at a minimum interval of 3-5
- mpMRI cannot be used as a stand-alone tool to trigger follow-up biopsies



Qualitative study on decision-making by prostate cancer physicians during active surveillance

Mark D. Schwartz. Herbert Lepor. Herbert Ballentine Carter. Erica Sedlande

Key Themes to Explain Heterogeneity in AS Practices

- Physician comfort with AS
- Protocol selection
- Beliefs about utility and quality of testing
- Years of experience and AS exposure in training
- Concerns about inflicting harm
- Patient characteristics
- Patient preferences
- Financial incentives

### Challenges with Monitoring During AS

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Prostate-Specific Antigen Kinetics During Follow-Up Are an Unreliable Trigger for Intervention in a Prostate Cancer Surveillance Program

Ashley E. Ross, Stacy Loeb, Patricia Landis, Alan W. Partin, Jonathan I. Epstein, Anna Ketterman Zhaoyong Feng, H. Ballentine Carter, and Patrick C. Walsh

- Changes in PSA not reliable (AUC 0.59 for biopsy reclassification)
- Guidelines still recommend routine surveillance biopsy every 1-5 years

Challenges with Monitoring During AS

- MRI is not recommended as a replacement for repeated prostate biopsy
- Biopsy-based AS presents significant risks and patient burden
  - $-\uparrow$  infections over time due to antibiotic resistance
  - Other risks: bleeding, pain, urinary symptoms, possible erectile dysfunction
  - Source of noncompliance

Ross et al. JCO 2010; 28: 2810. Nam et al. J Urol 2010; 183: 963. Loeb et al. J Urol 2011; 186: 1830. Loeb et al. Eur Urol 2013; 64: 876

### Biopsies During AS (SEER-Medicare)

Tests received by 1349 men on AS for 5y	% of patients
PSA	
≥5 PSA (yearly)	91%
≥10 PSA (2x/yr)	59%
Biopsy	
≥2 biopsies	34%
≥3 biopsies	15%
Combination	
≥10 PSA + ≥2 biopsies	22%

Strategies to improve adherence:

•More tools/resources to support men on AS

•More noninvasive testing options (e.g. markers and MRI)

•Individualizing the protocol based upon risk factors

Loeb et al. J Urol 2016 epub.

### Markov Model: Design

Comparison of Strategies in the	f Conservative Management ne Model
Watchful Waiting	No testing. No treatment unless metastatic disease.
AS- Johns Hopkins	PSA every 6 months and annual biopsy. Treat if grade progression on biopsy.
AS- PRIAS	PSA every 3 months. Repeat biopsy after 1, 4, and 7 years. Treat for grade progression.
AS Exploratory- MRI Based	PSA every 6 months and yearly MRI. Biopsy if MRI is positive. Treat for grade progression.
AS-5 year biopsy	PSA every 6 months and biopsy every 5 years.  Treat if grade progression.

Platinum Priority - Prostate Cancer Editorial by XXX on pp. x-y of this issue

Active Surveillance Versus Watchful Waiting for Localized Prostate Cancer: A Model to Inform Decisions

Stacy Loeb "h.", Qinlian Zhou", Uwe Siebert "Azef, Ursula Rochau", Beate Jahn", Nikolai Mühlberger", H. Ballentine Carter", Herbert Lepor", R. Scott Braithwaite

Model starting at 50yo	Incremental life-years	Incremental quality- adjusted life-years	Lifetime metastasis	Lifetime prostate cancer death
Watchful waiting			10.3%	8.7%
AS- Hopkins (1yr bx)	+0.66	+0.53	6.4%	5.4%
AS- PRIAS (bx yrs 1,3,7,10)	+0.57	+0.44	7.1%	6.0%
AS- MRI-based	+0.65	+0.53	6.4%	5.4%
AS- Biopsy every 5y	+0.44	+0.27	8.2%	6.9%

Platinum Priority - Prostate Cance Editorial by XXX on pp. x-y of this iss

Active Surveillance Versus Watchful Waiting for Localized Prostate Cancer: A Model to Inform Decisions

Stacy Loeb "A.\*", Qinlian Zhou b, Uwe Siebert "ded, Ursula Rochau", Beate Jahn", Nikolai Mühlberger", H. Ballentine Carter", Herbert Lepor", R. Scott Braithwaite b

	Incremental QALY- 40yo	Incremental QALY- 50yo	Incremental QALY-65yo	Incremental QALY-70
Watchful waiting				
AS- Hopkins	+0.89	+0.53	-0.10	-0.31
AS- PRIAS	+0.73	+0.44	-0.10	-0.28
AS- MRI-based	+0.90	+0.53	-0.10	-0.32
AS- Biopsy q5y	+0.49	+0.27	-0.13	-0.18

•Among men aged >65 yr, AS still had a small increase in life-years but WW had more QALYs

ORIGINAL ARTICLE

WILEY The Prostate

When should active surveillance for prostate cancer stop if no progression is detected?

Tiago M. de Carvalho Msc | Eveline A. M. Heijnsdijk PhD | Harry J. de Koning PhD

- · Microsimulation model based on Hopkins AS
- Low-risk patients:
  - Ages 55-65: AS is cost-effective for up to 7 yearly biopsy rounds
  - Age >65: Even 1 biopsy round results in QALYs lost
- Intermediate-risk:
  - AS is cost-effective even at ages 65-75

### Outline

- Rationale and utilization trends
- Barriers to uptake of active surveillance
- · Outcomes of active surveillance

### The NEW ENGLAND JOURNAL of MEDICINE OCTOBER 13, 2016

10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer

F.C. Hamdy, J.L. Donovan, J.A. Lane, M. Mason, C. Metcalfe, P. Holding, M. Davis, T.J. Peters, E.L. Tu R.M. Martin, J. Corley, M. Robinson, J. Staffurth, E. Walsh, P. Bollina, J. Catto, A. Doble, A. Doherry, D. G. R. Kockelbergh, H. Kynaston, A. Paul, P. Powell, S. Pescocat, D.J. Rosario, E. Rowe, and D.E. Neal, for the Protect Study Group<sup>®</sup>

- Active "monitoring" with PSA kinetics
  - More men developed metastases
  - No difference in prostate cancer death

Long-Term Outcomes of Sunnybrook AS (Canada)

- n=993 enrolled since 1995
  - -79% low risk, 21% intermediate risk
- Treatment-free: 76% at 5y, 64% at 10y, 55% at 15y
- 30 (3%) developed metastasis,15 Pca deaths (1.5%)
- At 15 years:
  - -94% cancer-specific survival
  - -9x more likely to die from other causes vs prostate cancer

Klotz et al. JCO 2014; 33: 272 Yamamoto et al J Urol 2016; 195: 1409

### Long-Term Outcomes of Hopkins AS (USA)

- N=1298 enrolled since 1995
  - -71% very low risk, 29% low-risk PCa
- Treatment-free: 63% at 5y, 50% at 10y, 43% at 15y
- At 15 years:
  - -99.4% metastasis-free survival
  - -99.9% PC-specific survival
  - -24x more likely to die of other causes than to develop metastasis or death from prostate cancer

Tosoian et al. JCO 2015: 33: 3379.

### AS in Goteborg Screening Trial (Sweden)

- N=474 managed by AS (no predefined protocol)
  - 51% very low, 27% low, 22% intermediate-risk
- % treatment free: 47% at 10y, 34% at 15y
- At 15 years:
  - 93% metastasis-free survival
  - 96% cancer-specific survival
    - 100% very low risk, 96% low risk, 90% intermediate-risk
  - 51% overall survival

Godtman et al. Eur Urol 2016 epub

### Modeling Studies of AS

- Compared to initial treatment, AS is associated with:
  - -Slightly higher rate of prostate cancer death
    - 2.8% at 20 years (AS), versus 1.6% (treatment)
  - -Greater quality-adjusted life-expectancy
  - -Lower costs

Xia et al. Clin Cancer Res 2012; 18: 5471. Hayes et al. JAMA 2010; 304: 2373. Eldefrawy et al. Urol Oncol 2013; 31:576.

### Conclusion

- Increasing use of active surveillance worldwide
  - Persistent variability and barriers to uptake
- Recommended option for low-risk prostate cancer
  - Majority remain on surveillance >5y
  - Low rate of metastasis within 15y
  - Greater risk of death from other causes than PCa
  - Cost-effective
- Future improvement with greater personalization and integration of noninvasive tests

### **W** UROLOGY

### **Prostate Cancer Biomarkers**

Todd M. Morgan, MD
Associate Professor
University of Michigan

### **UROLOGY**

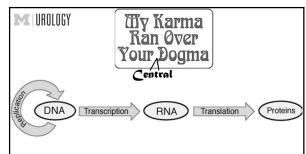
### **Disclosures**

- Myriad Genetics: Research funding, advisory board
- MDxHealth: Research funding, advisory board
- GenomeDx: Research funding

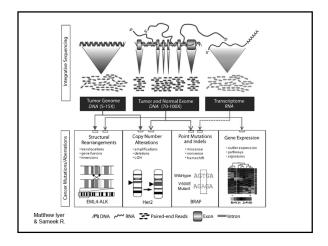
### **W** UROLOGY

### **Definitions**

- Genetics: Study of single/limited number of genes and their functions
  - Often used to refer to heritable mutations
- Genome: All of the genes in an individual
- Genomics: Study of the genome
- Epigenetics: Study of changes to DNA that don't involve change in nucleotide sequence
- Proteomics: Large-scale study of proteins



- 2% of genome codes for protein
- 98% "dark matter"
  - $\boldsymbol{\rightarrow}$  Majority of dark matter still transcribed (IncRNA, miRNA, piRNA. . .)



### **W** UROLOGY

# Why do we care? Biomarkers can help with...

- Risk assessment: what is the probability of disease?
- Screening: can earlier diagnosis affect outcome?
- Diagnosis: is the disease present?
- Prognosis: what is the likely outcome?
- Prediction: outcome in the presence of specific treatment?
- Monitoring: is therapy working?

### UROLOGY

## Personalization of Therapy Prognostic vs Predictive Biomarkers

- Nearly all cancer biomarkers are <u>prognostic</u> biomarkers that provide information on outcomes *independent of the* treatment received.
- A <u>predictive</u> biomarker specifically identifies response or resistance to a particular therapy – but not all treatments.
- Both are used to personalize therapy







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### The ideal biomarker

- · Safe and easy means of assessment
- Optimal statistical associations with intended outcome (e.g., high sensitivity, specificity, positive and negative predictive value)
- Provides clinically useful information that guides decision making

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### **Process for evaluating biomarkers**

- Analytical validity: does the assay accurately measure what it is intended to measure
- Clinical validity: does the assay identify a clinically relevant biological difference
- Clinical utility: do the results of the assay impact the plan of care and improve outcomes



# EDRN approach to validation Figure 1 Guiding Principles for Biomarker Research: Phases of Early Detection Research Phase 5 Cancer Control Evaluate both the role of the biomarkers for detection of cancer and the overall impact of screening on the population through large-scale population studies

Phase 4 Prospective Screening
Identify the extent and characteristics of disease detected
by the test and determine the false referral rate
hase 3 Retrospective Longitudinal
Determine how well biomarkers detect preclinical disease by testing the

hase 2 Clinical Assay and Validation

Studies to determine the capacity of biomarkers to distinguish between people with capacity and those without

markers against tissues collected longitudinally from research cohorts

Phase 1 Preclinical Exploratory
Exploratory studies to identify potentially useful biomarkers

### **W** UROLOGY

# Assessing performance of diagnostic tests

• Validity of a diagnostic test refers to its ability to measure what it is purported to measure.

Table 1. Standard table for comparison of test results with actual disease status

	Disease Present	Disease Absent	
Test Positive	a (true positives)	<b>b</b> (false positives)	a+b
Test Negative	c (false negatives)	d (true negatives)	c+d
	040	b±d.	a+b+a+d

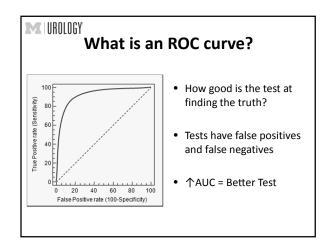
Sensitivity =  $\mathbf{a} / (\mathbf{a} + \mathbf{c})$ Specificity =  $\mathbf{d} / (\mathbf{b} + \mathbf{d})$ Accuracy =  $\mathbf{a} + \mathbf{c} / (\mathbf{a} + \mathbf{b} + \mathbf{c} + \mathbf{d})$ Positive Predictive Value =  $\mathbf{a} / (\mathbf{a} + \mathbf{b})$ Negative Predictive Value =  $\mathbf{d} / (\mathbf{c} + \mathbf{d})$ 

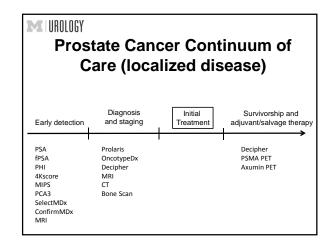
From Penson/Wei ed: Clinical Research Methods for Surgeons 2006

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### PPV and NPV are key

- Positive Predictive Value (PPV): Given that a test is positive, PPV is the probability that this patient actually has the disease
- Negative Predictive Value (NPV): Given that a test is negative, NPV is the probability that this patient actually does not have the disease





### **W** UROLOGY

# Sources of prostate cancer biomarkers

- Urine
  - Can be post-DRE
- Blood
  - Few currently used markers outside of PSA and PSA derivatives
- Sputum
  - Source for germline DNA
- Tissue
  - Biopsy or surgical specimen (FFPE)

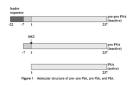
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### **Early Detection**

### **W** UROLOGY

### **PSA**

- Secreted protein first studied in 1970s
- Serine protease (kallikrein 3)
- Secreted into semen
- Mature PSA comes from 2 proteolytic cleavages (pre-proPSA and proPSA)



### **M** UROLOGY

### **PSA performance characteristics**

- Screening:
  - Specificity: 20-40%
  - Sensitivity: 70-90%
  - AUC 0.55-0.70
- Key flaw is confounding by BPH and variability between tests
  - Similar expression by BPH and PCa cells

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### **PSA** derivatives

- PSA velocity (PSAV): Cutoff of 0.75 ng/ml/yr sometimes used in screening setting
- PSA doubling time (PSADT): http://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx
- PSA density (PSAD): Cutoff of 0.15 ng/ml/cc often used
- Age-specific PSA cutoffs (2.5, 3.5, 4.5, 6.5 ng/ml)

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### Free PSA

- Unbound PSA (α1-antichymotrypsin)
- Lower %fPSA/tPSA = higher PCa risk
- FDA approved for use in patients with PSA of 4-10 ng/ml (Catalona et al, 1998 JAMA)

Free:total PSA ratio	Rates of prostate cancer			
	50-59 years	60-69 years	≤70 years	
≤0.10	49.20%	57.50%	64.50%	
0.11-0.18	26.90%	33.90%	40.80%	
0.19-0.25	18.30%	23.90%	29.70%	
>0.25	9.10%	12.20%	15.80%	

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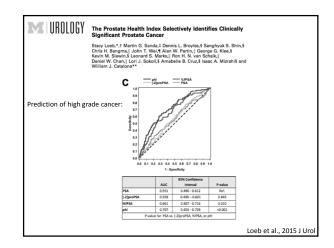
### **Prostate Health Index (PHI)**

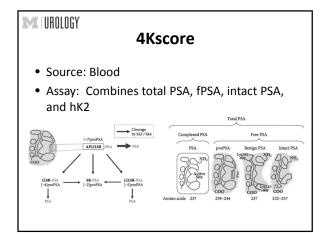
• Source: Blood

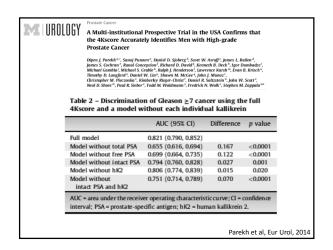
• Assay: Combines PSA, fPSA, [-2]proPSA

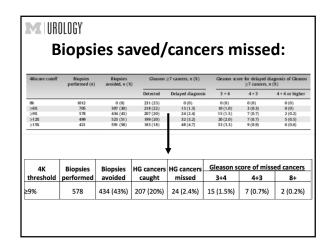
- ([−2]proPSA/fPSA) x  $\sqrt{PSA}$ 

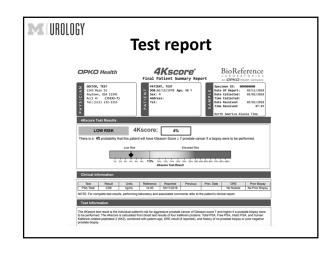
- FDA approved for PCa diagnosis in patients with PSA 4-10 ng/ml
- [-2]proPSA is precursor to active PSA

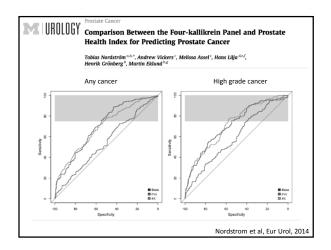


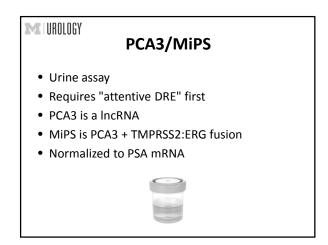


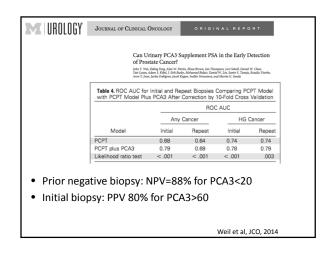


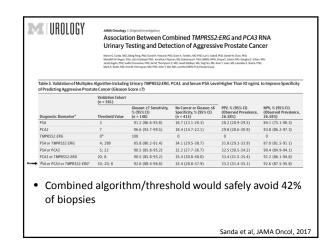


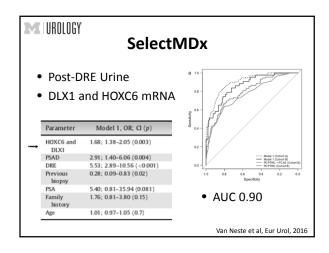


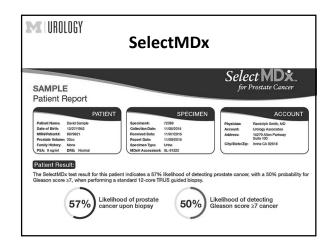


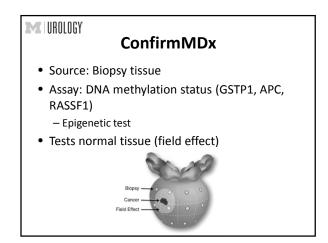


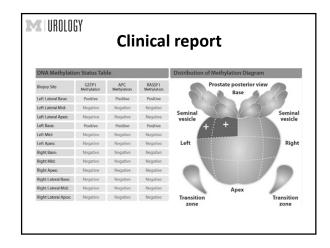


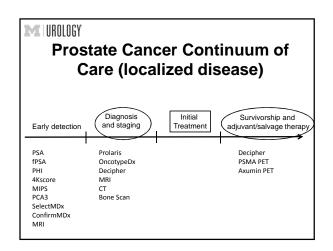


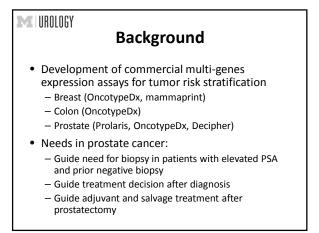


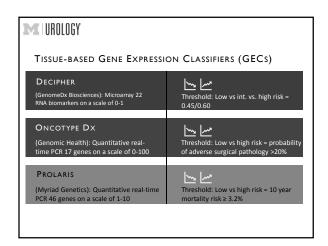


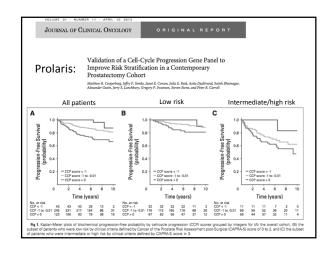


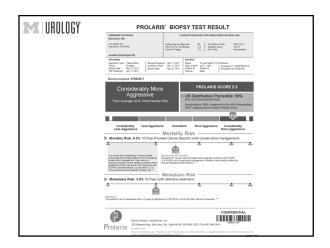


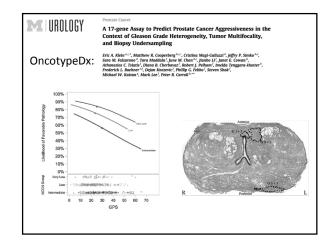


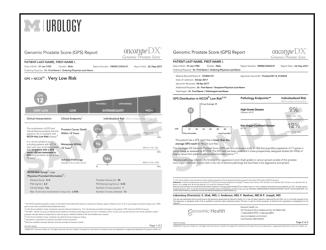


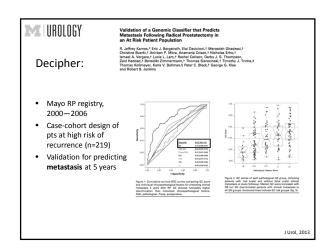


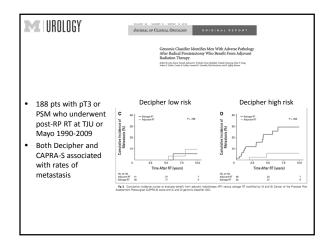


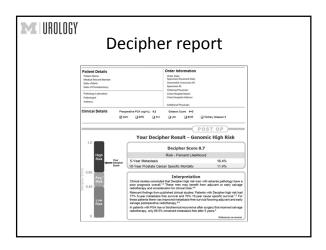


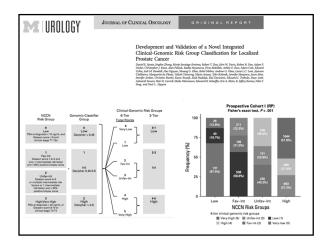


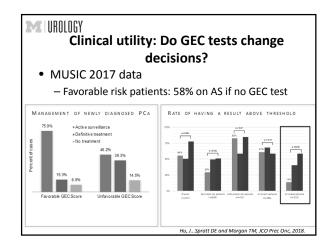


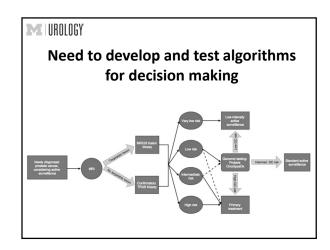


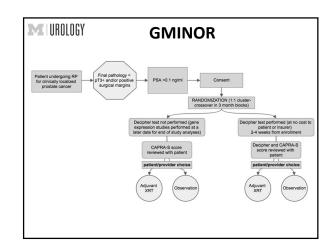


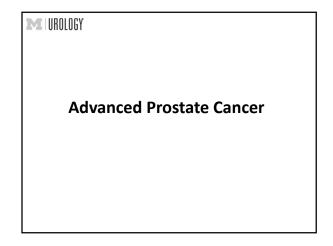


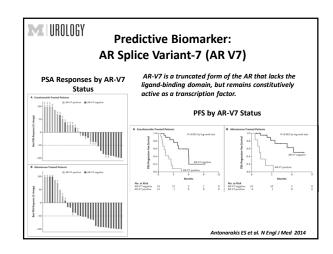


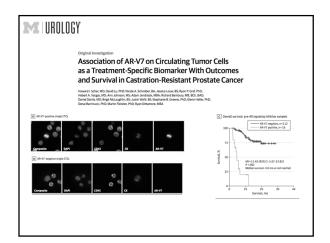


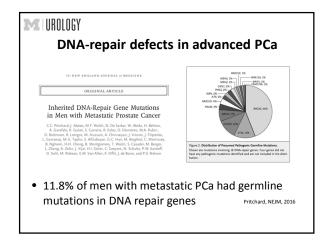


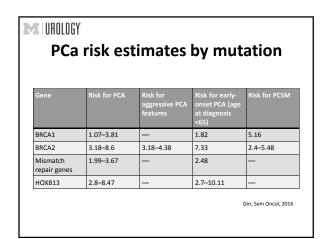


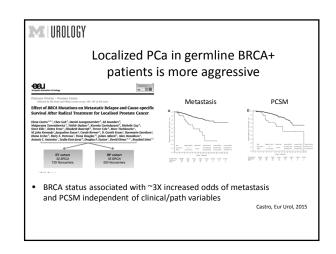


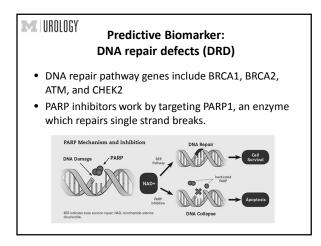


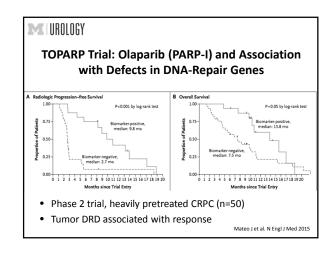


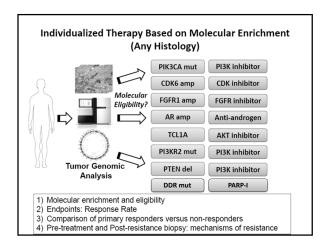






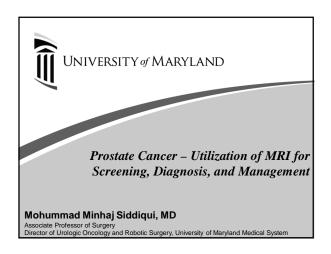


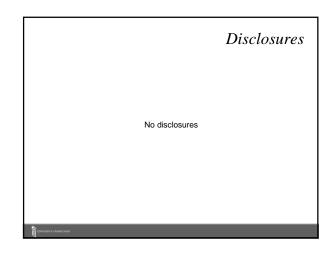




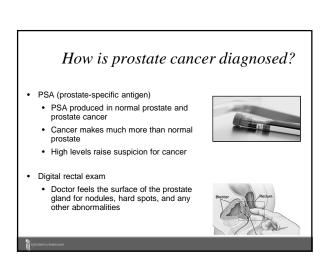
### M | UROLOGY Summary

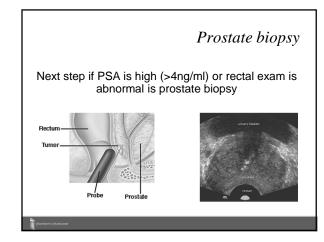
- · Know what's available in each disease setting
- Consider whether additional information will impact decision
- · Understand what each test is predicting
- Distinction between prognostic and predictive markers is key
- Be critical of data with each new test that is commercialized and marketed

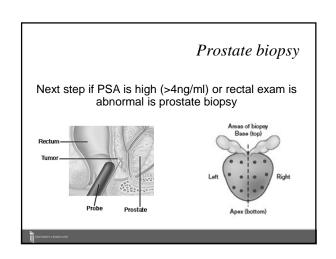


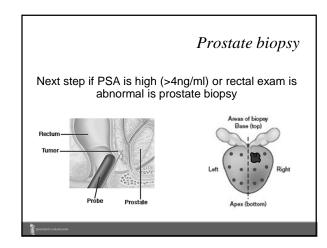


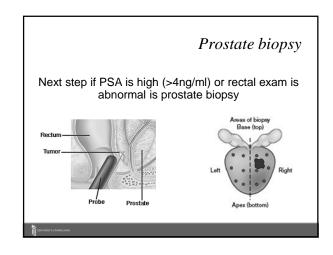
# Most common cancer in men 233,000 new cases in the US in 2014 1 in 6 men will be diagnosed with prostate cancer in their life Second leading cause of cancer death in US men Male Cancer Incidence Rates 1975 to 2009 Peak year 1992 Peak year 1992 Peak year 1992 Peak year 1992 Peak year of Diagnosis

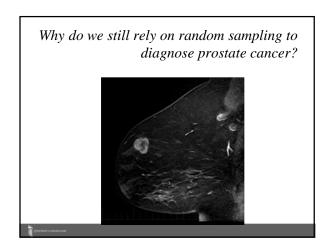


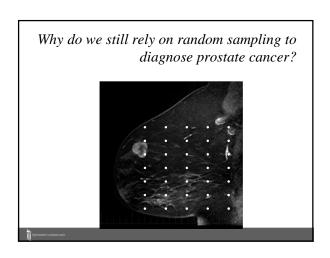


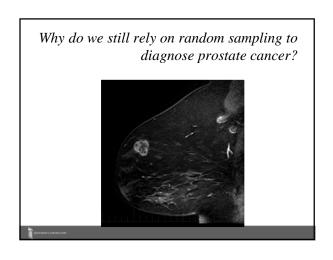


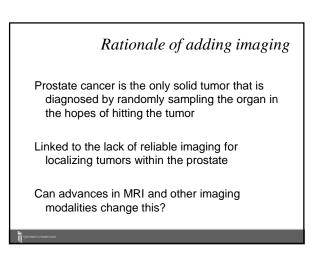




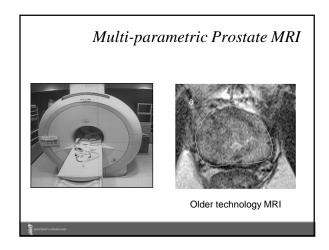


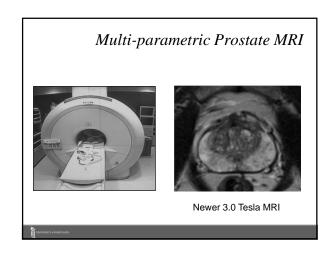


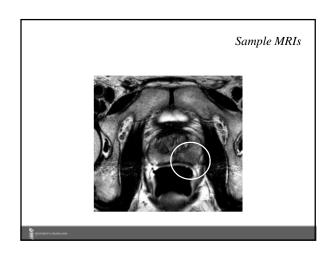


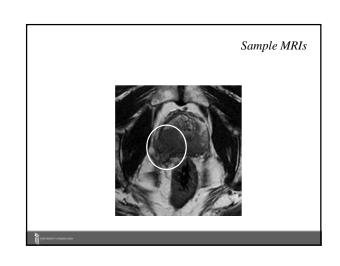


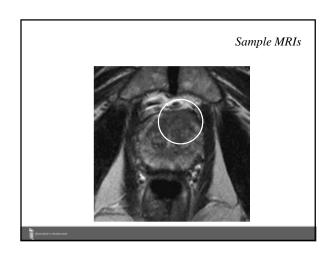
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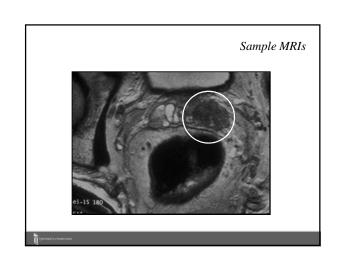


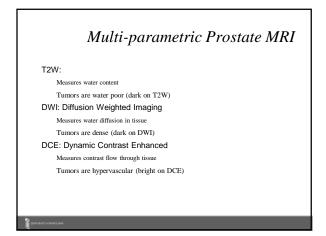


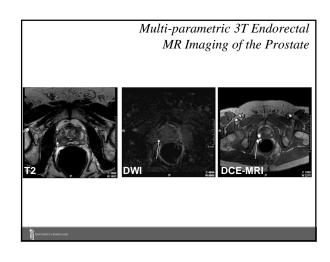


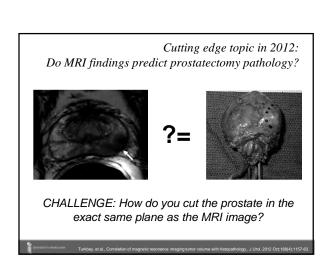


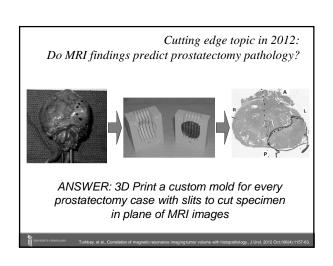


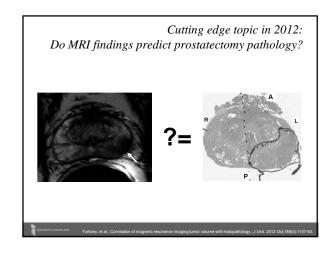


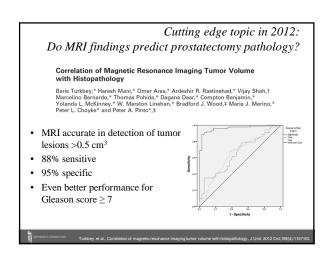












# PIRADS Prostate Imaging and Reporting and Data System ESUR prostate MR guidelines 2012 • Guidelines for MRI in PCa • Clinical indications, minimal/optimal MRI techniques • PI-RADS structured reporting system • Rates the likelihood of the presence of clinically significant prostate cancer • Score of 1-5 for T2, DWI/ADC, DCE, MRS, extra-prostatic

Barentsz JO et al. European Radiology 2012;22:746-57

PIRADS v2
Prostate Imaging and Reporting and Data System

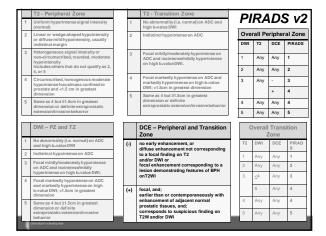
PIRADS v2 introduced at RSNA 2014
Promote standardization, decrease variation in acquisition, interpretation and reporting
Improve detection, localization, characterization, risk stratify

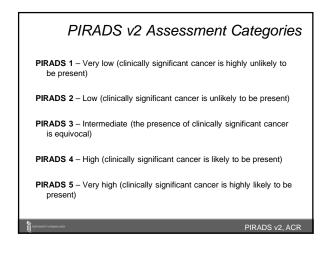
More specific criteria for T2 and DWI scoring

• PZ: DWI is dominant sequence

• TZ: T2 is dominant sequence

MRS is not included in scoring





Use of MRI to guide biopsies

"Cognitive fusion"

In gantry biopsy

MRI/US fusion biopsy

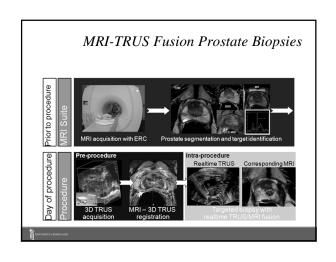
Use of MRI to guide biopsies

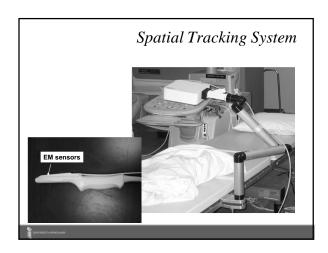
"Cognitive fusion" - inaccurate

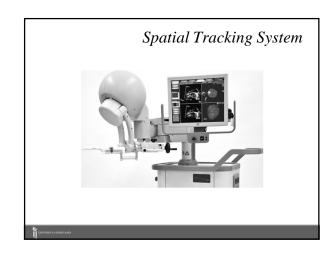
In gantry biopsy

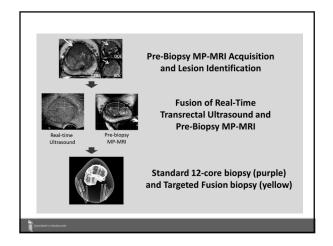
MRI/US fusion biopsy

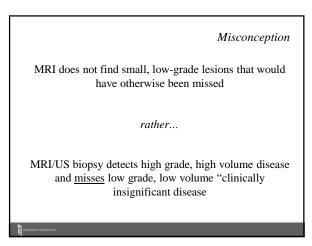
# Use of MRI to guide biopsies "Cognitive fusion" - inaccurate In gantry biopsy – resource intensive MRI/US fusion biopsy



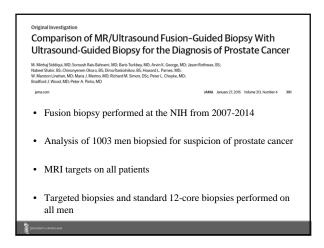


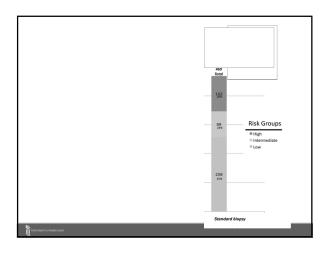


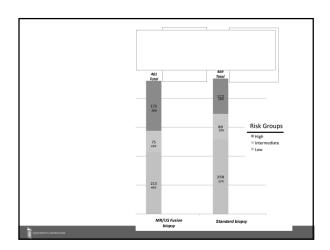


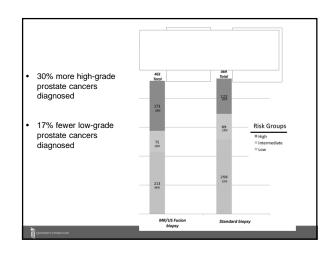


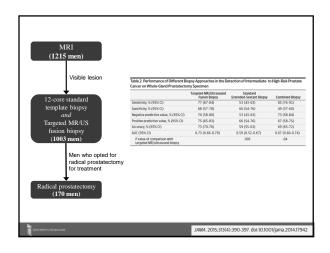
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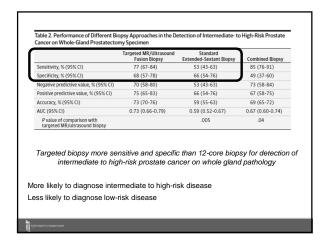


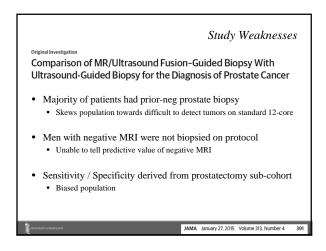


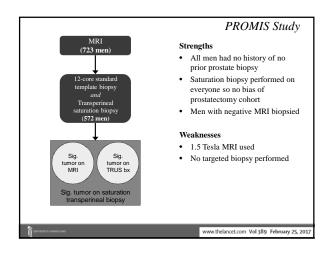


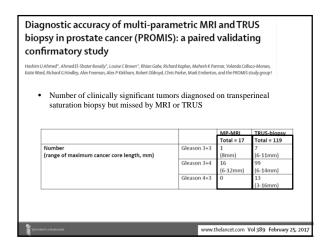


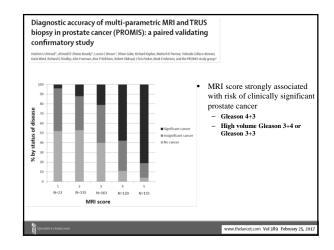


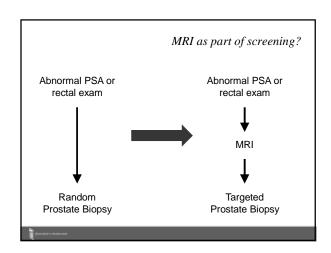


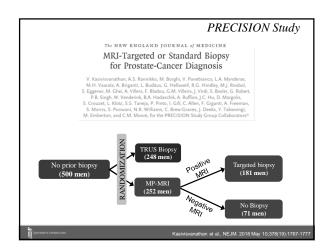




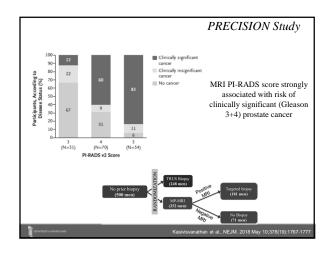


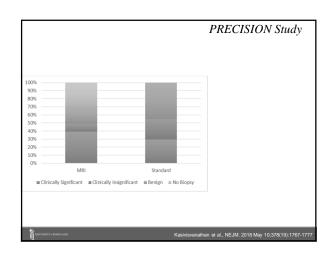


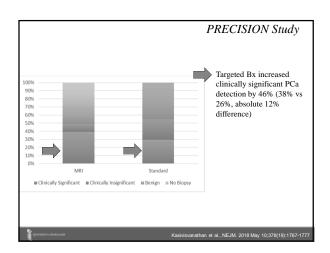


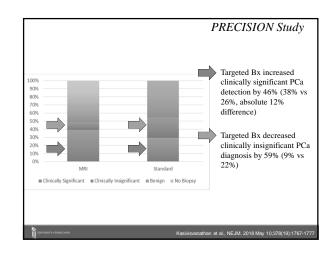


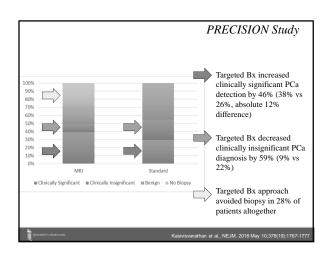
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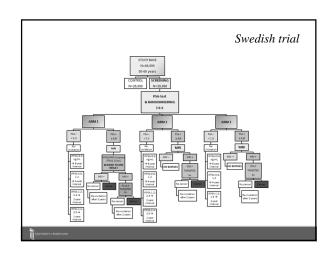


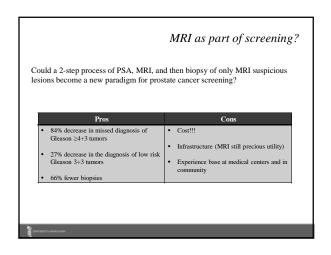


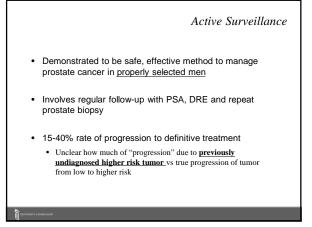


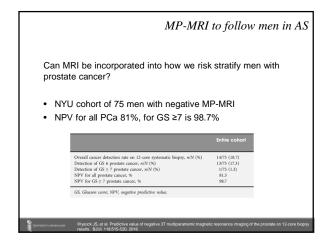


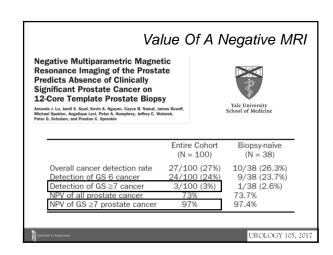


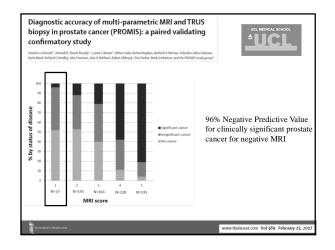


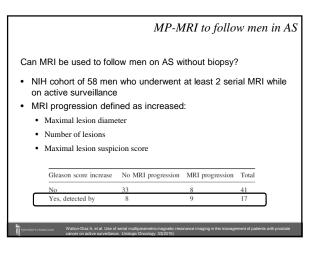












### MP-MRI to follow men in AS

- NIH series: Poor performance of MRI progression to predict pathologic progression (53% sensitivity)
- UCLA series: 49 men, more stringent definition of MRI progression, similarly poor association of MRI progression to predict pathologic progression (37% sensitivity)
- Although MRI may be predictive of intermediate/high risk prostate cancer, changes in MRI may not be as sensitive to progression

Felker ER, et al. Serial Magnetic Resonance Imaging in Active Surveillance of Prostate Cancer: Incremental Value Ely. J Urology. 195(1421-1427) May 2016

Walton-Diaz A, et al. Use of serial multiparametric magnetic resonance imaging in the management of patients with prostate

Provocative questions for MRI and active surveillance

Can MRI be incorporated into how we risk stratify men with prostate cancer?

Yes

Can MRI be used to follow men on AS without biopsy?

No!

### 3D printing to assist surgical planning











3D Model used intraoperative to assist with resection of prostate and attention to tumor margins

UNIVERSITY # MARIE

### Guidance for radical prostatectomy



- Retrospective case-control study of 134 men with MRI, 134 without, who underwent RARP
- Positive margin rate with MRI = 7.5%
- Positive margin rate no MRI = 18.7%, p=0.01
- Multivariate analysis controlling for Gleason score, surgeon, nerve sparing, age, PSA and stage shows MRI still significantly reduces positive margin rate

Petrala G, Musi G, Padhani AR et al. Robot assisted Radical Prostatectomy: Multiparametric MR Imaging-directed Intraoperative Frozen-Section

### Extracapsular extension

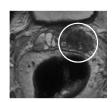


- Retrospective review of 169 men who had radical prostatectomy and preop MRI
- Extracapsular extension seen in 53 (23%)

Performance of MRI for d	etecting ECE
Sensitivity	48.7%
Specificity	73.9%
Positive Predictive Value	35.9%
Negative Predictive Value	82.8%

Raskolnikov D et al. The Role of Magnetic Resonance image Guided Prostate Biopsy in Stratifying Men for Risk of Extracapsular Extens at Radical Prostatectomy. J Urol Jul 2015. 194(1) 105-111

### Seminal Vesicle Invasion



- Review of 822 men with MRI and targeted MR/US fusion biopsy
- 25 had concern for SV invasion on MR
- 6 had concern for bilateral SV invasion
- 31 SV's sampled on biopsy, 20 (65%) were positive

RASKOINIKOV D et al. Multiparametric magnetic resonance imaging and image-guided bio

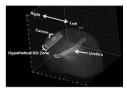
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# MRI-guided focal prostate cancer therapy?

20% of prostate cancer is unifocal

MRI with MR/US fusion biopsy gives greater confidence in distribution of tumor

Some patients with low risk disease are unable to reliably follow-up or are uninterested in active surveillance

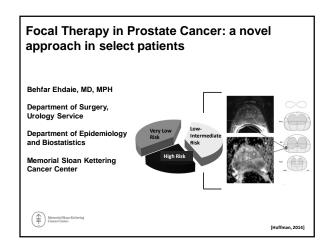


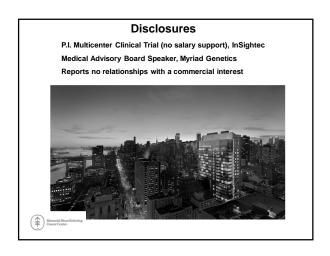
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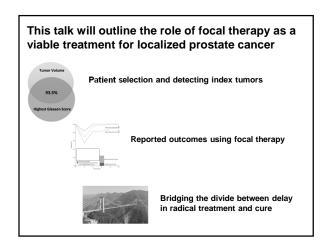
### Take away points

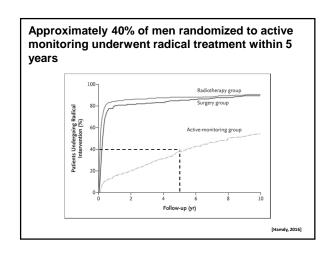
- MRI can detect regions of concern for prostate cancer
- MRI/US fusion guided biopsies more reliably can sample the prostate for detection of significant cancer
- The role of MRI guided treatment has promise but needs further development

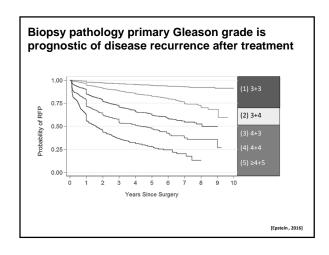
UNIVERSITY & MARYLAN

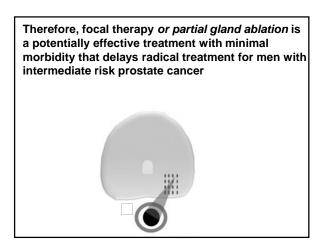


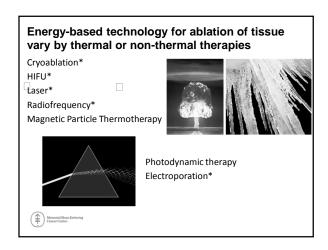


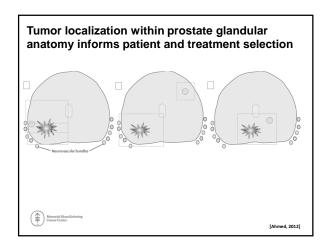


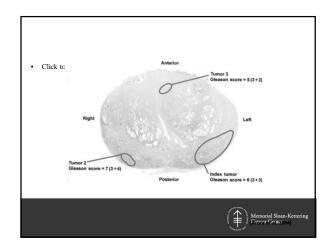


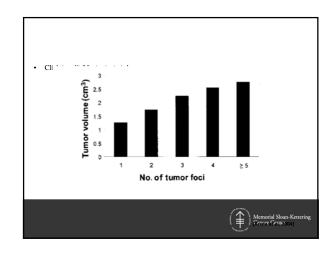


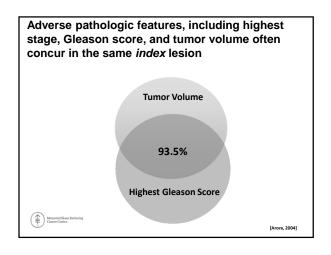


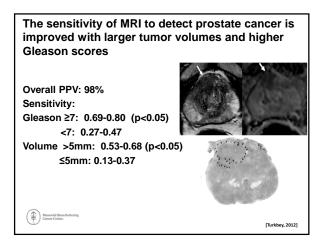


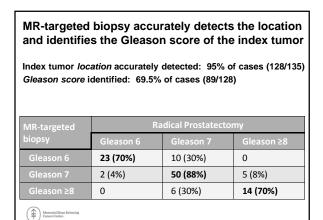


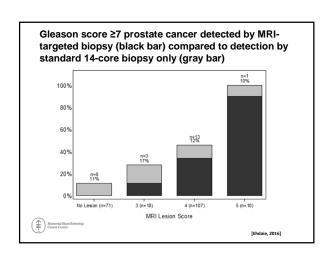


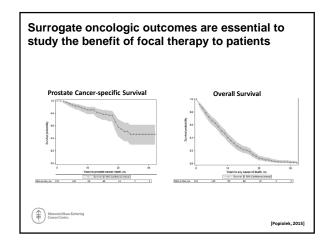


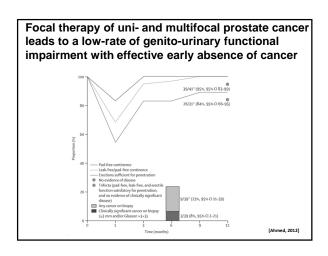


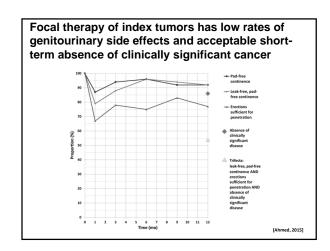


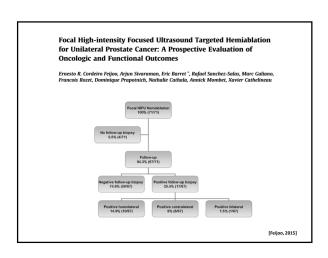


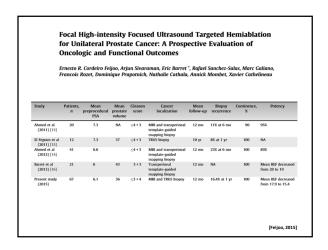


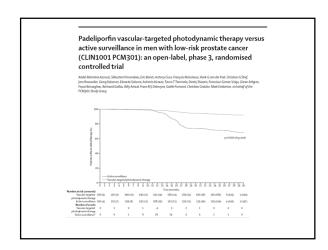


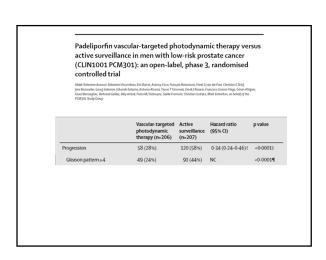


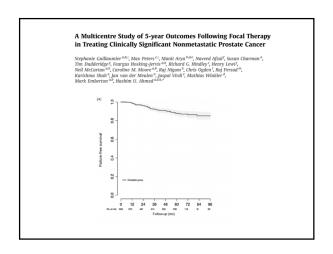






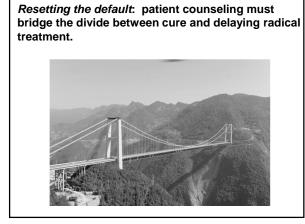


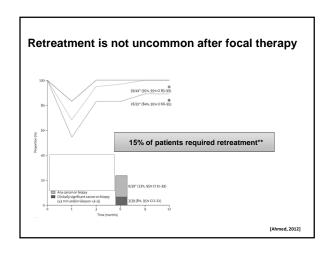


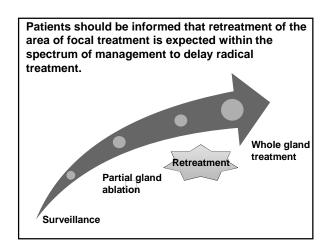


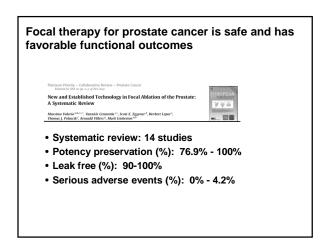
A Multicentre Study of 5-year Outcomes Following Focal Therapy in Treating Clinically Significant Nonmetastatic Prostate Cancer

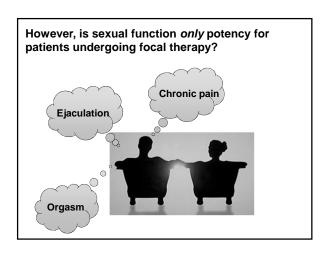
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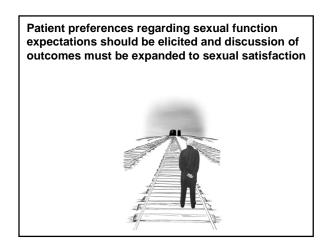


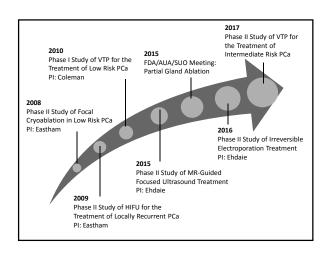


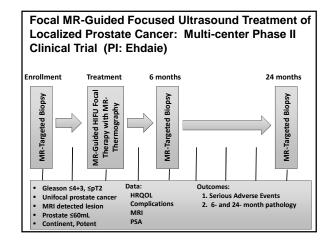


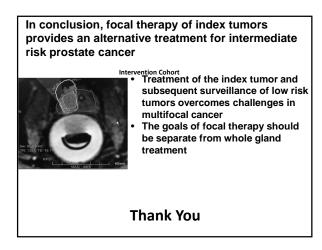












## Prostate Cancer: Surgical Management



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Siteman Cancer Center
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St. Louis, Missouri

## Disclosures

- Clinical Investigator:
- Nanospectra, FKD Therapies, Pfizer
- Consultant/Advisor:
- Augmenix, 3D Biopsy, Stratify Genomics, Janssen, Astellas, Blue Earth Diagnostics Inc.
- Research Support:
- National Cancer Institute
  - NIH-NIDDK
  - Peter Michael Foundation
  - St. Louis Men's Group Against Cancer
  - Barnes-Jewish Hospital Foundation
  - Mid-West Stone Institute

### Surgical Treatment of Prostate Cancer: Outline of talk

- · Evidence that it works
- · Patient Selection
- Tumor Factors
- · Pelvic Lymphadenectomy
- · Radical Prostatectomy
  - Open
  - Perineal
  - Laparoscopic + Robotic Assistance

### Surgical Treatment of Prostate Cancer: Outline of talk

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  - Open
  - Perineal
  - Laparoscopic + Robotic Assistance

# Randomized Trials of Radical Prostatectomy

• SPG-4: Pre-PSA era

• PIVOT: Early PSA screening era

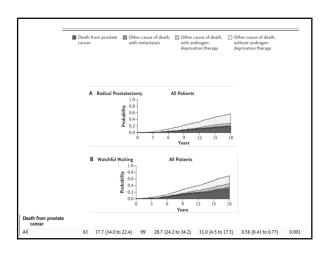
• PROTECT: Contemporary PSA screening

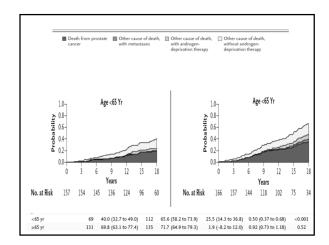
Radical Prostatectomy or Watchful Waiting in Early Prostate Cancer

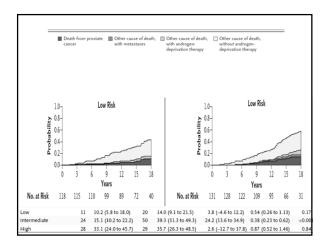
Anna Bill-Assison, M.D., Ph.D., Lars Holmberg, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Rider, S.C.D., Kimmo Taris, M.D., Ph.D., Christer Busch, M.D., Ph.D., Sign Nordling, M.D., Ph.D., Michael Higgman, M.D., Ph.D., D.D., Soren-Olof Andersson, M.D., Ph.D., Anders Spingberg, M.D., Ph.D., Walder, M.D., Ph.D., D., Ove Andre, M.D., Ph.D., Hans-Glov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D., Ph.D., Wans-Glov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D.

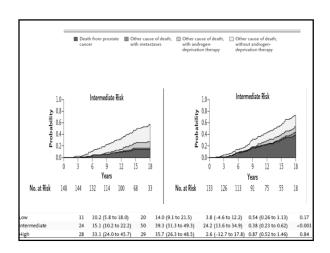
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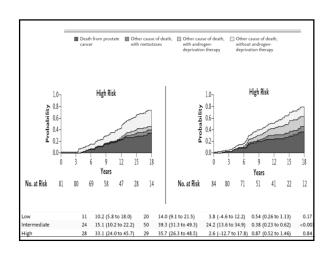
End Point		Cumulativ	e Incider	nce	Absolute Risk Reduction with Radical Prostatectomy	Relative Risk with Radical Prostatectomy (95% CI)	P Value
	Radio	tal Prostatectomy (N=347)	W	atchful Waiting (N=348)			
	no. of events	% (95% CI)	no. of events	% (95% CI)	percentage points (95% CI)		
Death from any cause							
All	200	56.1 (50.9 to 62.0)	247	68.9 (63.8 to 74.3)	12.7 (5.1 to 20.3)	0.71 (0.59 to 0.86)	< 0.001
Age							
<65 yr	69	40.0 (32.7 to 49.0)	112	65.6 (58.2 to 73.9)	25.5 (14.3 to 36.8)	0.50 (0.37 to 0.68)	< 0.001
≥65 yr	131	69.8 (63.1 to 77.4)	135	71.7 (64.9 to 79.3)	1.9 (-8.2 to 12.0)	0.92 (0.73 to 1.18)	0.52
Tumor risk							
Low	51	43.4 (34.8 to 54.1)	85	59.1 (50.7 to 68.8)	15.6 (2.5 to 28.8)	0.57 (0.40 to 0.81)	0.002
Intermediate	87	57.1 (49.0 to 66.4)	95	72.5 (64.5 to 81.6)	15.5 (3.3 to 27.6)	0.71 (0.53 to 0.95)	0.02
High	62	73.3 (63.8 to 84.2)	67	78.8 (69.7 to 89.2)	5.6 (-8.5 to 19.6)	0.84 (0.60 to 1.19)	0.34
Death from prostate cancer							
All	63	17.7 (14.0 to 22.4)	99	28.7 (24.2 to 34.2)	11.0 (4.5 to 17.5)	0.56 (0.41 to 0.77)	0.001
Age							
<65 yr	31	18.3 (13.1 to 25.7)	58	34.1 (27.3 to 42.5)	15.8 (6.0 to 25.5)	0.45 (0.29 to 0.69)	0.002
≥65 yr	32	17.3 (12.5 to 24.0)	41	23.9 (18.2 to 31.5)	6.6 (-2.1 to 15.2)	0.75 (0.47 to 1.19)	0.19
Tumor risk							
Low	11	10.2 (5.8 to 18.0)	20	14.0 (9.1 to 21.5)	3.8 (-4.6 to 12.2)	0.54 (0.26 to 1.13)	0.17
Intermediate	24	15.1 (10.2 to 22.2)	50	39.3 (31.3 to 49.3)	24.2 (13.6 to 34.9)	0.38 (0.23 to 0.62)	< 0.001
High	28	33.1 (24.0 to 45.7)	29	35.7 (26.3 to 48.5)	2.6 (-12.7 to 17.8)	0.87 (0.52 to 1.46)	0.84

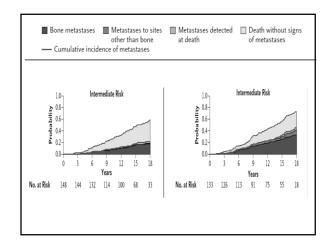


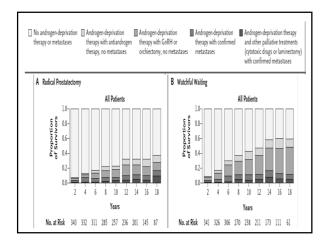


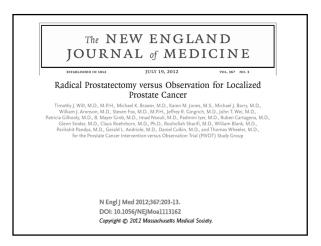












Follow-up of Prostatectomy versus
Observation for Early Prostate Cancer
Timothy J. Wilt, M.D., M.P.H., Karen M. Jones, M.S., Michael J. Barry, M.D.,
Gerald L. Andriole, M.D., Daniel Culkin, M.D., Thomas Wheeler, M.D.,
William J. Aronson, M.D., and Michael K. Brawer, M.D.

### **PIVOT Objective**

Among men with screen-detected, clinically localized prostate cancer during the "early" PSA era, does the intent to treat with radical prostatectomy reduce all-cause &/or prostate cancer mortality compared to observation?

### **Inclusion Criteria**

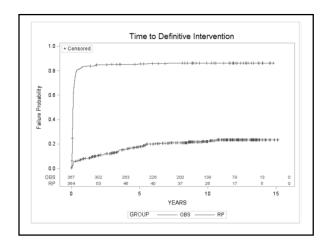
- Age ≤ 75 years
- T1-2, NX, M0 (all histologic grades)
- PSA < 50 ng/mL
- Diagnosed ≤ 12 months
- Radical Prostatectomy candidate
  - Predicted life expectancy > 10 years

### **Endpoints**

- Primary endpoint

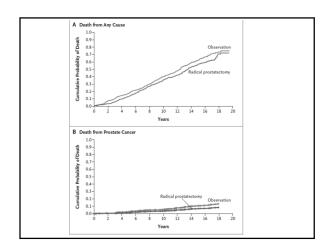
   All-cause mortality
- Secondary endpoint -CaP mortality

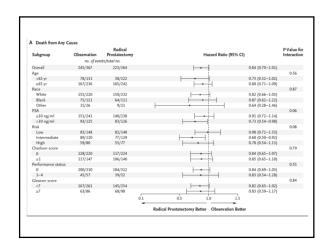
Tumor C	haracteris	STICS
Characteristic	<b>Observation</b>	<u>RP</u>
<ul> <li>PSA Mean (median)</li> </ul>	10.2 (7.8)	10.1 (7.8)
<b>- &lt; 4.0 (%)</b>	10.9	11.5
- <u>≥</u> 20 (%)	10.1	10.4
<ul> <li>Stage: T1c (%)</li> </ul>	49.9	50.8
<ul> <li>Gleason Score (%)</li> </ul>		
<u>&lt;</u> 6	70.1	69.8
7	17.4	19.0
8-10	6.0	8.0
<ul> <li>D'Amico Tumor Risk</li> </ul>	•	
Low	40.3	40.7
Intermediate	32.7	35.4
High	21.8	21.2

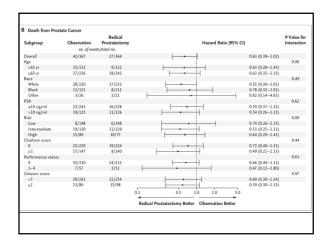


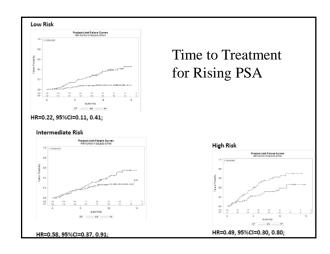
### Follow-up & Cumulative Events

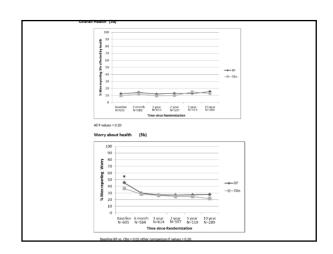
- · Median follow-up
  - 12.7 years (IQ range 12 to 19.5 years)
- All-cause mortality
  - **-468/731 (64.1%)**
  - Higher than expected
- Prostate cancer mortality
  - **-69/731 (9.4%)**

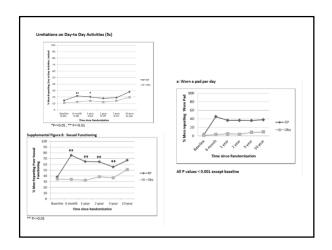








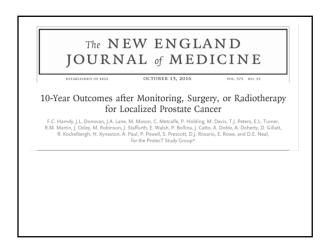


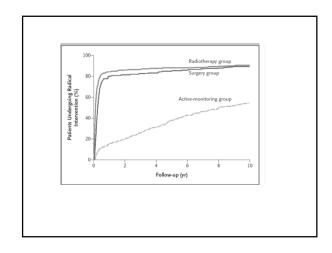


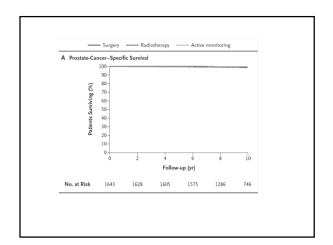
### Criticisms of PIVOT

- Volunteers were sicker than most RP series
  - Higher death rate than anticipated
- Underpowered
  - Designed for 2000 patients
  - Need ~1500 pts. for 80% power
- Crossover/Non-compliance further dilutes power
  - ~20% in each arm

	PIVOT	SPG-4
F-up (yr)	19.5	23.2
Death (%)	64	64
CaP Death (%)	9.4	29







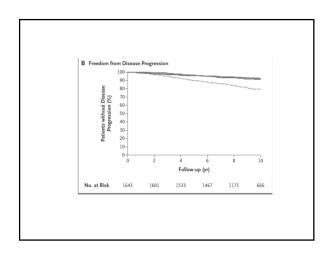


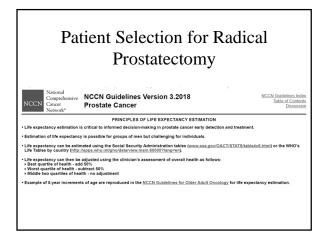
Table 1. Prostate-Cancer Mortality, Incidence of Clinical Progression and Metastatic Disease, and All-Cause Mortality, According to Randomized Treatment Group.							
Variable	Active Monitoring (N = 545)	Surgery (N = 553)	Radiotherapy (N = 545)	P Value			
Prostate-cancer mortality							
Total person-yr in follow-up	5393	5422	5339				
No. of deaths due to prostate cancer†	8	5	4				
Prostate-cancer–specific survival — % (95% CI)†							
At 5 yr	99.4 (98.3-99.8)	100	100				
At 10 yr	98.8 (97.4-99.5)	99.0 (97.2-99.6)	99.6 (98.4-99.9)				
Prostate-cancer deaths per 1000 person-yr (95% CI)†	1.5 (0.7-3.0)	0.9 (0.4-2.2)	0.7 (0.3-2.0)	0.48			
Incidence of clinical progression:							
Person-yr of follow-up free of clinical progression	4893	5174	5138				
No. of men with clinical progression	112	46	46				
Clinical progression per 1000 person-yr (95% CI)	22.9 (19.0-27.5)	8.9 (6.7-11.9)	9.0 (6.7-12.0)	< 0.001			
Incidence of metastatic disease							
Person-yr of follow-up free of metastatic disease	5268	5377	5286				
No. of men with metastatic disease	33	13	16				
Metastatic disease per 1000 person-yr (95% CI)	6.3 (4.5-8.8)	2.4 (1.4-4.2)	3.0 (1.9-4.9)	0.004			

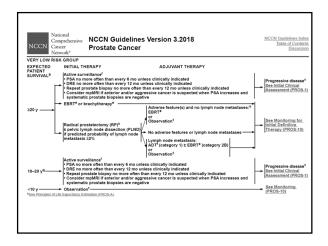
	SPG-4	PIVOT	Klotz	PROTECT
Years	1989-1999	1994-2002	1995-	1999-2009
Intervention	RP v WW	RP v Obs	AS	RP or XRT v AS
# Biopsy cores	?????	6	????	10
# Randomized	695 (Unk)	731 (15%)	????	1643 (62%)
Age (mean)	<75 (65)	<75 (67)	<90 (68)	50-69 (61)
% White	????	62	????	99
Mean PSA	13	10	5.2	5.8
Clin T1c	11	50	78	76
Gleason <7	60	74	84	77

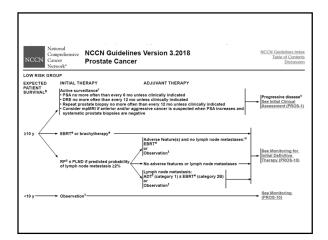
	PIVOT	SPG-4	Klotz	Protect
F-up (yr)	10	10.8	6.4	10
Death (%)	48	45	15	11
CaP Death (%)	7	19	3	1.5

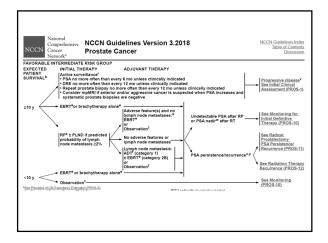
### Surgical Treatment of Prostate Cancer: Outline of talk

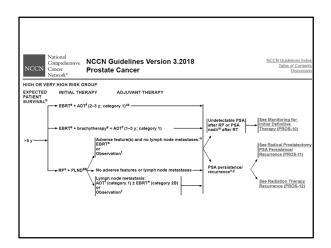
- Evidence that it works
- Patient Selection
- · Tumor Factors
- Pelvic Lymphadenectomy
- · Radical Prostatectomy
  - Open
  - Perineal
  - Laparoscopic  $\underline{+}$  Robotic Assistance











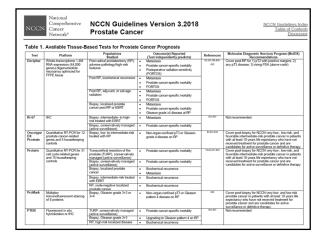
### **Predicting Life Expectancy**

- Challenging
- Over-estimates more common than underestimate
- Need better tools

### Surgical Treatment of Prostate Cancer: Outline of talk

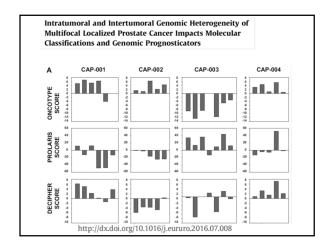
- Evidence that it works
- Patient Selection
- Tumor Factors
- Pelvic Lymphadenectomy
- Radical Prostatectomy
  - Open
  - Perineal
  - Laparoscopic + Robotic Assistance

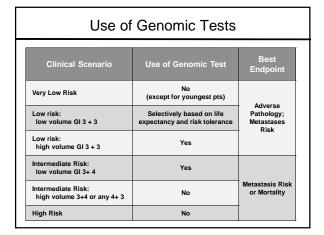
NCCN	National Comprehensive Cancer Network*  NCCN Guide Prostate Can	lines Version 3.2018 cer			uidelines Inde ble of Conten Discussion
	RISK	STRATIFICATION AND STAGING WORK	(UP		
Risk group	Clinical/pathologic features	Imaging <sup>i,j</sup>	Molecular testing of tumor	Germline testing	Initial therapy
Very low <sup>g</sup>	Tic AND     Gleason score SSigrade group 1 AND     PSA <10 rg/lml, AND     Fewer than 3 prostate biopsy fragment/cores positive, SSO% cancer in each fragment/core* AND     PSA density <0.15 rg/lml.gr	Not indicated	Not indicated	Consider if strong family history <sup>6</sup>	See PROS-4
Lowe	T1-T2a AND     Gleason score ≤6/grade group 1 AND     PSA <10 ng/ml.	Not indicated	Consider if life expectancy ≥10y	Consider if strong family history	See PROS-5
Favorable intermediate <sup>a</sup>	T2b-T2c CR     Gleason score 3+4+7/grade group 2 CR     PSA 10-20 rights, AND     Percentage of positive biopsy cores <50%	Bone imaging*: not recommended for staging     Pelvic ± abdominal imaging: recommended if nomogram precides > IO% probability of pelvic lymph node involvement	Consider if life expectancy ≥10y	Consider if strong family history <sup>6</sup>	See PROS-6
Unfavorable intermediate	T2b-T2c OR     Gleason score 3+4=7/grade group 2 or Gleason score     4+3=7/grade group 3 OR     PSA 10–20 ng/ml,	Bone imaging <sup>k</sup> : recommended if T2 and PSA > 10 ng/ ml.     Pelvic ± abdominal imaging: recommended if nomogram predicts > 10% probability of pelvic lymph node involvement.	Not routinely recommended	Consider if strong family history <sup>6</sup>	See PROS-7
High	T3a OR     Gleason score &igrade group 4 or Gleason score     45=5igrade group 5 OR     PSA >20 ng/m.	Bone imaging <sup>h</sup> : recommended     Pelvic a abdominal imaging: recommended if nomogram predicts > 10% probability of pelvic lymph node involvement	Not routinely recommended	Consider <sup>a</sup>	See PROS-8P
Very high	T3b-T4 OR     Primary Gleason pattern 5 OR     >4 cores with Gleason score 8–10/ grade group 4 or 5	Bone imaging*: recommended     Pelvic ± abdominal imaging: recommended if nomogram predicts > 10% probability of pelvic lymph node involvement	Not routinely recommended	Consider <sup>a</sup>	See PROS-8 <sup>p</sup>
Regional	Any T, N1, M0	Already performed	Consider tumor testing for homologous recombination gene mutations and for microsatelitie instability (MSI) or mismatch repair deficiency (dMMR)	Consider <sup>®</sup>	See PROS-9
Metastatic	Any T, Any N, M1	Already performed	Consider tumor testing for homologous recombination gene mutations and for MSI or dMMR <sup>m.h</sup>	Consider <sup>o</sup>	See PROS-13



### **Tissue Genomic Markers**

- All validated
- All have significant effect on treatment decisions
- · Never compared!



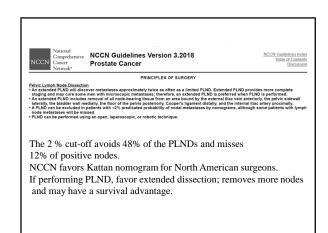


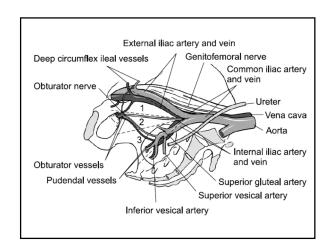
## Staging of Clinically Localized CaP

- PET imaging (eg, Gallium-PSMA) has shown some promise to identify occult metastases in "high-risk" otherwise localized CaP
  - Suspicious nodes identified in 25% pts (Rad. 288:495, 2018)
- May also identify intraprostatic disease better than multiparametric MRI

### Surgical Treatment of Prostate Cancer: Outline of talk

- · Evidence that it works
- Patient Selection
- Tumor Factors
- · Pelvic Lymphadenectomy
- · Radical Prostatectomy
  - Open
  - Perineal
  - Laparoscopic + Robotic Assistance





		o. of Predictors		Prevalence of LNI, %	Predictive accuracy, %
Cagiannos et al [42]	7,014	PSA, clinical stage, biopsy Gleason score	Limited	3.7	76
Kattan et al [4,10,11,33,51]	697	PSA, clinical stage, biopsy Gleason score	Limited	8	76.8
Makarov et al [12]	5,730	PSA, clinical stage, biopsy Gleason score	Limited	1	88
Briganti et al [13,41,53,55]	602	PSA, clinical stage, biopsy Gleason score	Extended	11	76
Briganti et al [13,41,53,55]	278	PSA, clinical stage, biopsy Gleason score, percentage of positive cores	Extended	10.4	83
Bluestein et al [14]	1,632	PSA, clinical stage, biopsy Gleason score	Limited	NA	NA
Bishoff et al [43]	481	PSA, clinical stage, biopsy Gleason score	Limited	7.7	NA
Narayan et al [44,45]	932	PSA, biopsy Gleason score	Limited	11	NA
Conrad et al [54,15]	344	No. of positive biopsies, no. of biopsies containing any Gleason grade 4 or 5 cancer	Limited	8.1	NA
Roach et al [45]	212	PSA, biopsy Gleason score	Limited	17	NA
Crawford et al [9,46,47]	4,133	PSA, clinical stage, biopsy Gleason score	Limited	NA	NA
Batuello et al [46,47]	6,135	PSA, clinical stage, biopsy Gleason score	Limited	4.6	81
Han et al [8,47,48]	5,744	PSA, clinical stage, biopsy Gleason score, age	Limited	5	88
Poulakis et al [49]	201	PSA, clinical biopsy Gleason score, and pelvic coil MRI findings	Limited	10	91
Karam et al [50]	425	PSA, clinical stage, biopsy Gleason score, preoperative plasma endoglin	Limited	3.3	97.8
Wang et al [51]	411	PSA, clinical biopsy Gleason score, and pelvic coil MRI findings	Limited	5	89.2
PLND: pelvic lymph node dis NA: not available	section, LNI	and pelvic coil MRI findings : lymph node invasion, PSA: prostate-specific anti	gen, MRI: n	nagnetic resona	nce imaging,

### Pelvic Lymphadenectomy for Prostate Cancer

- Adds some, but minimal, morbidity to RP
- Careful occlusion of lymphatic channels
  - Clips, energy sources
- Post-op drain if extrapertioneal RP; lymphocele may still occur if transperitoneal but is less frequent
- Possible therapeutic benefit to extended template lymphadenectomies

### Surgical Treatment of Prostate Cancer: Outline of talk

- · Evidence that it works
- · Patient Selection
- Tumor Factors
- Pelvic Lymphadenectomy
- · Radical Prostatectomy
  - Perineal
  - Open Retropubic "Anatomic"
  - Laparoscopic <u>+</u>Robotic Assistance

### Open Prostatectomy

- · Gold Standard
- Initially used perineal approach
- More recently, retropubic approach favored.
- Laparoscopic and Robotic-assisted techniques use the same principles of the open, retropubic "anatomic" approach

### Perineal Prostatectomy

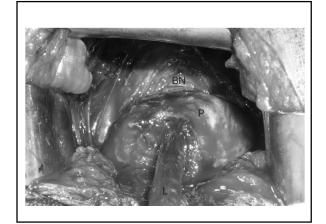
- · Bowel Prep pre-op
- Perform laparoscopic PLND if risk of involved nodes exceeds 2%
- Contraindicated if patient cannot be positioned in exaggerated lithotomy position (eg, ankylosing conditions) or if prostate is large (>100 gm)

### Perineal Prostatectomy Positioning









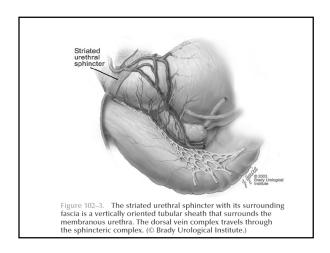
### Perineal Prostatectomy Outcomes

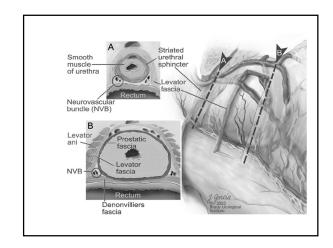
- Similar positive margin and PSA failure rates as other approaches
- In general, shorter operative time
- Neuropraxia rare (<2%)
- Transfusion rate ~ 5%
- Continence rates similar to other approaches
- Potency ranges from 35-70%

### Anatomic Prostatectomy

Open Retropubic, Laparoscopic and Robot-Assisted Laparoscopic techniques use the same principles articulated by Walsh et al.

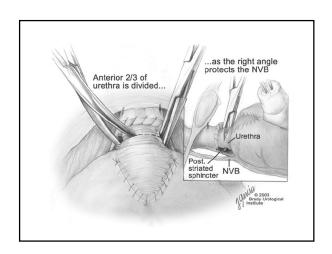
# Anatomic Prostatectomy Actural supply to biddistrated. (Sympathic) (Sympathic) (Participation) (Participation)

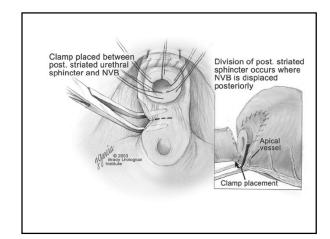


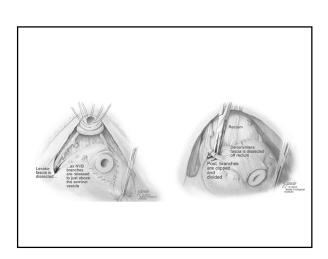


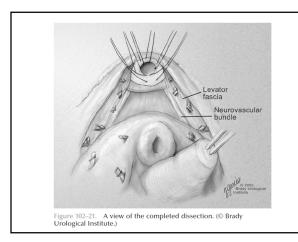
### Anatomic Prostatectomy: Steps

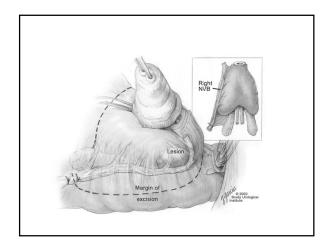
- Incise Endopelvic Fascia
- Divide the pubo-prostatic ligaments
- Preserve any accessory Pudendal arteries (~5% pts.)
- Suture ligate the dorsal venous complex
- Meticulous apical dissection after dividing DVC
- Retrograde dissection of the prostate





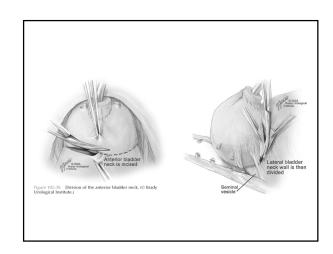






### When to excise the NVB

- Pre-OP
  - Extensive perineural invasion on biopsy
  - Large volume high grade disease
  - DRE or MRI suspicion of involvement
- Intra-Op
  - Induration of levator fascia
  - Tactile sense that NVB adherent to capsule

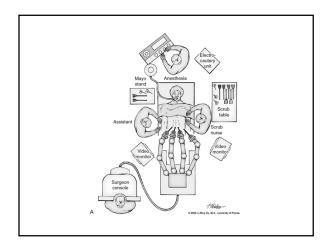


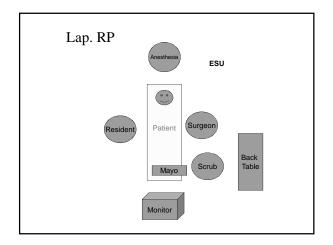
### Open Retropubic Prostatectomy

- Minimal mortality (0.2%)
- Thromboembolic events ~2%
- Bladder neck contracture 0.5-10%

### Open Retropubic Prostatectomy

- Bladder neck preservation
  - No to small benefit to time to continence
  - May have higher BN contracture rate and pos. margin rate
- Seminal Vesicle sparing
  - Concept is that SVI rarely extends more than 1 cm from prostate
  - Potentially less damage to pelvic nerves if SV tips left in situ
  - Data are ambiguous



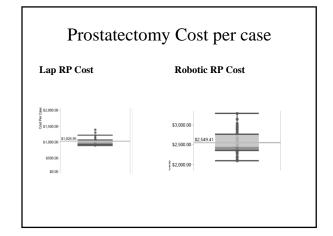


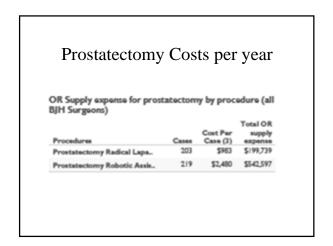
### Trans- v. Extraperitoneal Lap. RP

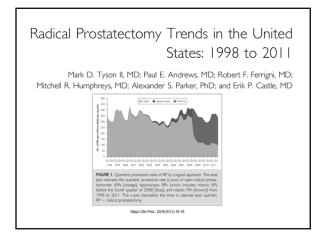
- Shorter OR time and hospital stay
- Easier positioning; minimal Trendelenburg
- · Less frequent need for adhesiolysis
- ?Less short-term bladder instability
- · ?Less long-term risk if post-op XRT
  - Open peritoneum may allow bowel to drop into pelvis, potentially compromising later pelvic XRT if warranted

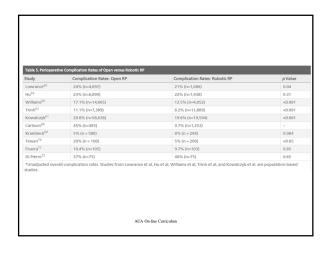
### Robot v. Pure Lap

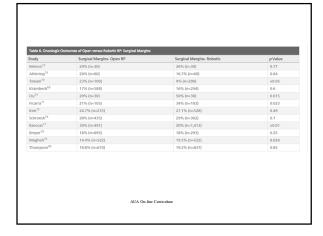
- Robot most often transperitoneal
- Robot more expensive
- Robotic surgeons lack tactile feedback
- Robotic surgeons rely on a potentially "rogue" bedside assistant
- Only the console surgeon has 3-D visualization v. entire OR team w pure lap

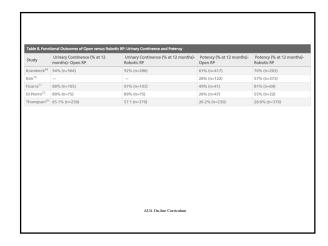








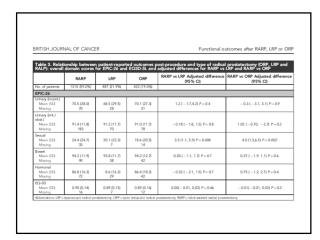




Robot-assisted radical prostatectomy vs laparoscopic and open retropubic radical prostatectomy: functional outcomes 18 months after diagnosis from a national cohort study in England

Results: In all, 2219 men (77.0%) responded; 1310 (59.0%) had RARP, 487 (21.7%) LRP and 422 (19.0%) ORP, RARP was associated with slightly higher adjusted mean EPIC-26 sexual function scores compared with LRP (3-5 point difference; 95% Ct. 1.1-5.9, P=0.000); which did not meet the threshold for a minimal clinically important difference (10-12 points). These were no significant difference in other EPIC-26 domain scores or HROQL.

Conclusions: It is unlikely that the rapid adoption of RARP in the English NHS has produced substantial improvements in functional outcomes for patients.



# The Australian laparoscopic non robotic radical prostatectomy experience – analysis of 2943 cases (USANZ supplement)

**Table 4** Oncological and Functional Outcomes of Australian LRP Series Compared to High-Volume Published Data of Open, Laparoscopic and Robotic Prostatectomy.

Variable	Our series	ORP*	LRP*	RALP*
pT2 (%)	73.6	64.3	64	78.7
pT3 (%)	26.2	31.5	32.6	20.5
pT2 PSM (%)	9.8	16.8	12.4	9.6
pT3 PSM (%)	32.6	42	39.2	37.1
Overall PSM (%)	15.9	24	21.3	13.6
Mean 12 month continence	91 <sup>†</sup>	80	85	92
Mean 12 month potency	47 <sup>‡</sup>	29	55	71

© 2016 The Authors
3JU International © 2016 BJU International | doi:10.1111/bju.13610
Published by John Wiley & Sons Ltd. www.bjui.org

### LRP: Personal Series

2235 through 2017Age: 62.1 +/-6.9

• BMI: 29.1 +/14.6

• PSA: 7.8 +/- 8.8

• 11% susp. DRE

• 93.6 % white

• 38% + Fam Hx

### LRP: Personal Series

• Op Time: 127 +/- 33 min.

• RP Gleason: 19% 6/65% 7/11% 8-10

• PSM: 7.4% T2/23% overall

• 15.4% PSA recurrence

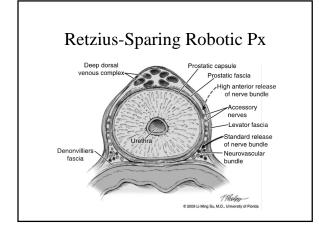
• Continence after 6 mon: 92%

• Erection after 1 year: 54.2% without meds

• 25.1% with meds

### Extraperitoneal Lap RP

- Combines advantages of open and robotic approaches in a cost-effective way
- Learning curve similar for all 3 approaches.



### Salvage Radical Prostatectomy

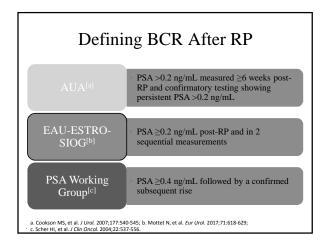
- Reserved for men in excellent health whose initial tumor was apt to be cured by surgery and whose re-staging after recurrence is also favorable.
- MRI and PET imaging (Choline or fluciclovine) recommended
- Intraoperative complications acceptable (~2% rectal injury)
- Continence in ~85% and potency up to 15%

### Salvage Radical Prostatectomy

- Oncologic outcomes:
  - Local control excellent
  - PSA recurrence in ~40% at 5 years
  - Uncertain impact on overall survival
- Most series use the open technique, but more recently laparoscopic and roboticassisted techniques are reported w similar outcomes

### Management of Post-Prostatectomy Biochemical Recurrence

- Current definition requires a PSA > 0.2
- Occurs in 20-30%
- Half of men destined to recur will do so within 3 years; 80% within 5 years and ~99% within 10 years
- Important considerations for treatment:
  - Interval between surgery and recurrence
  - Pathologic findings on RP
  - PSA kinetics



## Clinical Dilemmas in men with BCR

- Cannot tell where recurrent disease is located
- Absolute PSA levels tend to correlate with disease burden and risk for metastasis
- Shorter PSADT associated with higher risk of metastases
- Time to BCR is prognostic in most, but not all, studies

a. Darwish OM, et al. Front Oncol. 2012;2:1-6. b. Paller CJ, et al. Clin Adv Hematol Oncol. 2013;11:14-23

# Diagnostic Evaluation of Patients With BCR - No guidelines on frequency of evaluation in men with BCR - NCCN Guidelines® note: • Factors affecting BCR imaging use after RP - Risk group before surgery - Gleason score - Stage - Serum PSA - PSADT after recurrence • Cross-sectional imaging and conventional Tc-99m bone scans are rarely positive in asymptomatic men with PSA < 10 ng/mL • Imaging should be performed more frequently when PSADT ≤ 8 mo

NCCN (	Cancer Network	, I	Prostate	Cancer				NCC
Tracer	Half- life (min)	Cyclotron	Mechanism of action	Excretion	Sensitivity (%)*	Specificity (%)*	FDA Status	Panel Recommendation
C-11 choline	20	Onsite	Cell membrane synthesis	Hepatic	32-93	40-93	Cleared	May be used for detection of biochemically recurrent small-volume disease in soft tissues
F-18 fluciclovine	110	Regional	Amino acid transport	Renal	37-90	40–100	Cleared	May be used for detection of biochemically recurrent small- volume disease in soft tissues
F-18 NaF	110	Regional	Adsorption within bone matrix	Hepatic	87–100	62-89	Cleared	May be used after bone scan for further evaluation of equivocal findings
C-11 acetate	20	Onsite	Lipid synthesis	Lung	59-69	83-98	Not cleared	May be used in clinical trial or registry
Ga-68 PSMA	68	Generator (no cyclotron)	PSMA analog	Renal	76–86	86–100	Not cleared	May be used in clinical trial or registry

### <sup>11</sup>C-Choline-PET/CT Sensitivity by PSA Level

- Analysis of 358 patients post-RP with BCR (≥ 2 consecutive PSA measurements > 0.2 ng/mL)
  - · Overall sensitivity /specificity: 85% /93%
- Detection rate by PSA level:
  - PSA 0.2 to 1 ng/mL: 19%
  - PSA 1 to 3 ng/mL: 46%
  - PSA > 3 ng/mL: 82%
- Package insert for <sup>11</sup>C-choline notes reduced sensitivity and specificity in patients with PSA levels < 2.0 ng/mL</li>

a. Giovacchini G, et al. Eur J Nucl Med Mol Imaging. 2010;37:301-305

11C-Choline PET/CT in Patients With BCR Systematic Review								
Parameter, %	All 18 Studies (N = 2126)	10 Studies Reporting Local Recurrence (n = 993)	7 Studies Reporting Nodal Metastases (n = 752)	8 Studies Reporting Bone Metastases (n = 775)				
Pooled detection rate (95% CI)	62 (53, 71)	27 (16, 38)	36 (22, 50)	25 (16, 34)				
No. of studies assessable for sensitivity/specificity (pts, n)	12 (1270)	6 (491)						
Pooled sensitivity (95% CI)	89 (83, 93)	61 (40, 80)						
Pooled specificity (95% CI)	89 (73, 96)	97 (87, 99)						
Fanti S, et al. Eur J Nucl Med N	1ol Imaaina. 2016:43	:55-69.						

### 18F-Fluciclovine PET/CT in BCR PC: BED-001 Study

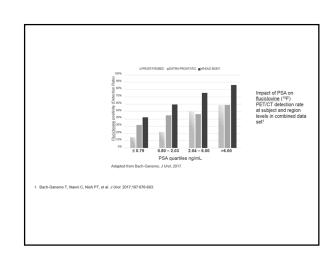
- Retrospective analysis of 18F-fluciclovine in 596 patients who received  $\geq\!\!1$  injection for the detection of suspected BCR after RP or RT
- Overall detection rate was 67.7%

### Detection Rate by Site

Site	Detection Rate, %
Prostate bed	38.7
Pelvic lymph nodes	32.6
Extrapelvic metastases	26.2

Overall detection rate for patients with PSA <0.8 ng/mL was 41.4%</li>

Bach-Gansmo T, et al. J Urol. 2017;197:676-683



# $\begin{array}{c} \text{Salvage Lymphadenectomy} \\ \\ \text{20} \\ \text{10} \\ \text{20} \\$

### Surgery for Prostate Cancer

- It works for the right patient and the right
- Approach-open, Lap or Robotic Asst Lap—doesn't seem to matter significantly in terms of outcomes; but cost of robotic approach significantly higher than others
- Salvage surgery after XRT or isolated nodal metastases reasonable in men whose initial tumor was curable.

### **Radiation For Prostate Cancer in the Definitive** and Post-Operative Setting

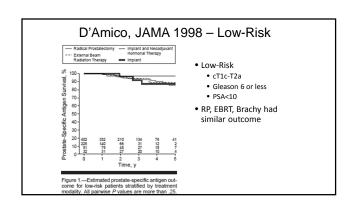
Paul L Nguyen, MD Vice Chair for Clinical Research Genitourinary Disease Center Leader for Radiation Oncology Dana-Farber/Brigham and Women's Cancer Center Associate Professor Harvard Medical School

### **Disclosures**

- Consulting:
  - Ferring
  - Augmenix
  - Bayer
  - Blue Earth Janssen
- Research Funding:
- Janseen, Astellas
- Equity
  - Augmenix

### NCCN Low-Risk Prostate Cancer - Many options

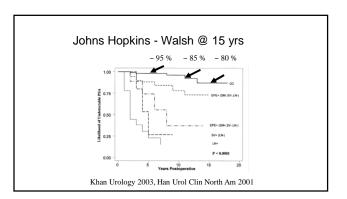
- Active Surveillance
- Radical Prostatectomy
- External Beam Radiation Alone (No Hormones)
  - Standard Course: 79.2Gy/1.8Gy per fraction (44 fxs), 78Gy/2Gy/fx (39 fxs)
  - Hypofractionated: 70Gy/2.5Gy per fx (28fxs), 60Gy/3.0Gy per fx (20fxs)
  - $\bullet$  SBRT: Stereotactic Body RT: 36-40Gy in five fractions of 7.25-8Gy
- Brachytherapy
   Low Dose Rate (Single permanent seed implant): I-125, Pd-103, Cs-131
  - High Dose Rate (Temporary Catheters, 4 fxs): Ir-192



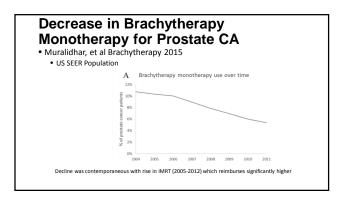
### Brachy Outcomes (Low-Risk)

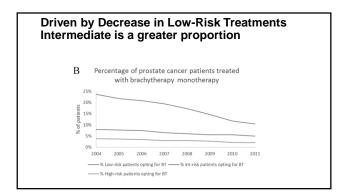
Study	n	PSA control	F/U (yrs)	
Merrick	160	97 %	5	~ 95 %
Zelefsky	319	96 %	5	75 70
Blasko	230	84 %	9	~ 85 %
Grimm	125	87 %	10	~ 65 70
Stone	279	78 %	10	
Potters	481	88 %	12	~ 80 %
Sylvester	215	86 %	15	

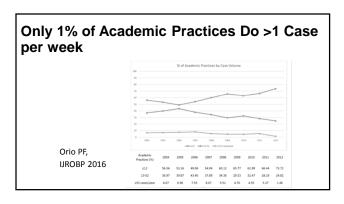
Merrick IJROBP 2001, Zelefsky IJROBP 2007, Blasko IJROBP 2000, Grimm IJROBP 2001, Stone J Urol 2005, Potters J Urol 2005, Sylvester IJROBP 2011

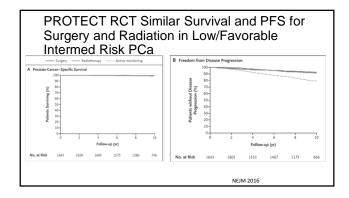


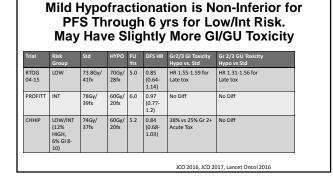












### **Model Policies** -ASTRO

### STEREOTACTIC BODY RADIATION THERAPY (SBRT)

Many clinical studies supporting the efficacy and safety of SBRT in the treatment of prostate cancer have been published. At least one study has shown excellent five year biochemical control rates with very low rates of serious toxicity. Additionally, numerous studies have demonstrated the safety of SBRT for prostate cancer after a follow-up interval long enough (two to three years) to provide an opportunity to observe the incidence of late GU or Glotoxicity. While it is necessary to observe patients treated for prostate cancer for extended intervals to gauge the rate of long term (beyond 10 years) biochemical control and overall survival, the interim results reported appear at least as good a other forms of radiotherapy administered to patients with equivalent risk levels followed for the same duration nost-treatment post-treatment.

It is ASTRO's opinion that data supporting the use of SBRT for prostate cancer have matured to a point where SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease.

Courtesy of Karen Hoffman, MD Anderson

### Randomized trials of SBRT vs. Conventional RT

- HYPO-RT-PC, Sweden, n=1200, Widmark
  - · Hypofractionated radiotherapy of intermediate/high risk and no ADT
  - 78 Gy in 2 Gy fractions vs. 42.7 Gy in 6.1 Gy fractions QOD over 2.5 weeks
  - Reported at ESTRO 2018 5yr FU,
  - Similar BRFS: 83.8% std vs. 83.7% SBRT bRFS HR=0.992 (0.735-1.307)
  - Similar Late Gr 2+ Urinary Tox: 3.5% std vs. 2.5% SBRT
  - Similar Late Gr 2+ Rectal Tox: 2.3% std vs. 1.3% SBRT.
- PACE Trial, UK, n=1700, Low/Int risk (RP vs. SBRT or Conv RT vs. SBRT)
  - 78 Gy in 2 Gy fractions vs. 36.25 in 7.25 Gy fractions
  - Nicholas Van As

### Intermediate-risk prostate cancer is a heterogeneous disease

- Unfavorable intermediate-risk: Gleason pattern 4+3=7,  $\geq$  50% biopsy cores, or multiple intermediate risk factors
- Favorable intermediate-risk: all others



### Trend towards avoiding ADT in **Favorable Intermediate Risk**

### Favorable:

### • Gleason 3+4

### • PSA <10

### OR • Gleason 6

### • PSA 10-20

### Unfavorable:

- Gleason 4+3
- >=50% of cores
- positive
- Multiple

intermediate factors

Favorable Intermediate Risk Can be Treated

like Low Risk Prostate CA

Zumsteg, et al Eur Urol 2013

### NCCN Favorable Intermediate Risk Prostate Cancer - Treat Like Low Risk

- Active Surveillance (But only for select cases)
- Radical Prostatectomy
- External Beam Radiation Alone (No Hormones)
  - Standard Course: 79.2Gy/1.8Gy per fraction (44 fxs), 78Gy/2Gy/fx (39 fxs)
     Hypofractionated: 70Gy/2.5Gy per fx (28fxs), 60Gy/3.0Gy per fx (20fxs)

  - SBRT: Stereotactic Body RT: 36-40Gy in five fractions of 7.25-8Gy
- Brachytherapy
  - Low Dose Rate (Single permanent seed implant): I-125, Pd-103, Cs-131
  - High Dose Rate (Temporary Catheters, 4 fxs): Ir-192

### French Experience w/Brachytherapy Monotherapy in Favorable Int. Risk

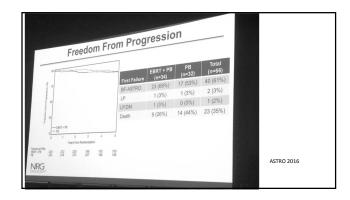
• Cosset, et al, IJROBP 2008

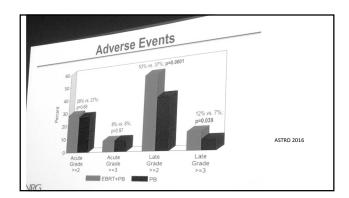
	5-yr bRFS
Low-Risk	97%
PSA 10-15, Gleas <=6	95%
PSA <10, Gleas 7	94%
PSA 10-15, Gleason 7	88%

Of note, D90s typically 180 in the series

# Supplemental EBRT is Not Needed With Brachy for Favorable Intermediate Risk

- RTOG 02-32 (Prestidge, ASTRO Plenary 2016)
  - N=588, "Favorable intermediate Risk"
  - cT1c-T2b w/GS6 & PSA10-20 or GS7 & PSA<10
    - 67% T1; 89% GS<=7 and PSA<10
  - Brachy alone (I-125 or Pd-103) vs. 45Gy EBRT + Brachy boost
  - Accrued, but closed for futility after 6.7 yrs and 443pts evaluable
  - PSA FFS was 85% for B+EBRT, and 86% for B
  - Late GU toxicity slightly higher in B+EBRT (7% vs. 3% late Gr. 3+ GU)





### **HDR Brachy as Monotherapy**

- HDR has been fully accepted as a boost but acceptance as monotherapy was slow due to lack of data
- $\bullet$  3 series published in 2016 led to NCCN guideline inclusion

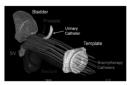
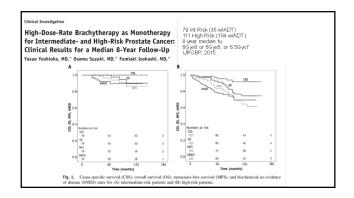
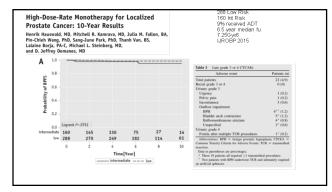


Fig. 1. Three-dimensional virtual image reconstruction of a high-dose-rate implant, with red representing source dwell positions. Abbreviation: SV, seminal vesicle.

i Saada Jawad, MD, " Joshua T. Dilworth, I S. Gustafson, MD, " Hong Ye, MS," Michel To Martinez, MD, FACR," Peter Y. Chen, MD Daniel J. Krauss, MD"	lle Wallace, BSN, OCN,"	32% Intermediate Risk 4.1 year median fu 4Gyx9, 12Gyx2, or 13.5Gyx2 UROBP, 2015			
Table 6 Clinical outcome	es for all patients at 5 years	24 C-12 (050) CV6	27 (2-12 (0)) (1) (1)		
Outcome	38 Gy/4 (95% CI, no. of patients at risk)	24 Gy/2 (95% CI, no. of patients at risk)	27 Gy/2 (95% CI, no. of patients at risk)	P valu	
Overall survival	98% (95.1-98.9, 177)	99% (91.0-99.8, 8)	100% (n/a, 1)	.55	
Cause-specific survival	100% (n/a, 176)	100% (n/a, 8)	100% (n/a, 1)	-	
Biochemical control	97% (93.5-98.7, 117)	87% (68-95.1, 5)	90% (63.8-97.6, 0)	.16	
Local control	91% (87.4-93.8, 160)	85% (70.0-92.6, 7)	81% (74.9-97.2, 0)	.45	
Distant metastases-free survival	100% (n/a, 177)	100% (n/a, 8)	100% (n/a, 1)	-	
Disease-free survival	89% (84.8-91.9, 160)	84% (69.2-91.6, 7)	91% (74.9-97.2, 0)	.32	

		38 Gy/4 n=319			24 Gy/2 n=79			27 Gy/2 n=96		
Toxicity	G1	G2	G3	GI	G2	G3	G1	G2	G3	P value
Frequency/urgency	42%	14%	3%	35%	18%	0%	43%	14%	1%	.62
Dysuria	25%	7%	0%	15%	6%	1.5%	22%	3%	0%	.11
Retention	16%	10%	1%	18%	5%	0%	14%	0%	0%	.07
Incontinence	5%	2%	0.4%	0%	0%	0%	1%	0%	0%	.18
Hematuria	5%	0%	0%	1.5%	1.5%	0%	0%	5%	0%	.004
Diarrhea	10%	2%	0%	8%	0%	0%	6%	0%	0%	.49
Rectal pain/tenesmus	5%	1%	0%	5%	0%	0%	0%	1%	0%	.31
Rectal bleeding	3%	0%	0%	3%	0%	0%	0%	0%	0%	.29
Proctitis										
	1% icity based	0.5% on dosing s	0%	0% all patients	0% (N=494)	0%	0%	1%	0%	.64
					0.10	0%		1% 27 Gy/2 n=96	0%	.64
		on dosing s 38 Gy/4			(N=494) 24 Gy/2	0% G3		27 Gy/2	0% G3	.64  P value
Table 3 Chronic tox	icity based	on dosing s 38 Gy/4 n=319	chedule for	all patients	(N=494) 24 Gy/2 n=79			27 Gy/2 n=96		
Table 3 Chronic tox	G1	on dosing s 38 Gy/4 n=319	G3	all patients	(N=494) 24 Gy/2 n=79 G2	G3	GI	27 Gy/2 n=96 G2	G3	P value
Table 3 Chronic tox  Toxicity  Frequency/urgency	G1	on dosing s 38 Gy/4 n=319 G2 19%	G3	all patients G1 37%	(N=494) 24 Gy/2 n=79 G2 23%	G3 0%	G1 44%	27 Gy/2 n=96 G2 20%	G3 3%	P value
Table 3 Chronic tox  Toxicity  Frequency/urgency Dysuria	G1 35% 18%	on dosing s 38 Gy/4 n=319 G2 19% 8%	G3 1% 1%	GI 37% 20%	(N=494) 24 Gy/2 n=79 G2 23% 3%	G3 0% 0%	G1 44% 24%	27 Gy/2 n=96 G2 20% 5%	G3 3% 4%	P value .31 .22
Table 3 Chronic tox  Toxicity  Frequency/urgency Dysuria Retention	G1 35% 18% 19%	on dosing s 38 Gy/4 n=319 G2 19% 8% 5%	G3 1% 1% 2%	G1 37% 20% 17%	(N=494) 24 Gy/2 n=79 G2 23% 3% 0%	G3 0% 0% 0%	G1 44% 24% 41%	27 Gy/2 n=96 G2 20% 5% 4%	G3 3% 4% 0%	P value .31 .22 .001
Table 3 Chronic tox  Toxicity  Frequency/urgency Dysuria Retention Incontinence	G1 35% 18% 19% 7%	on dosing s 38 Gy/4 n=319 G2 19% 8% 5% 2%	G3 1% 1% 2% 0.8%	GI 37% 20% 17% 13%	(N=494) 24 Gy/2 n=79 G2 23% 3% 0% 3%	G3 0% 0% 0% 0%	G1 44% 24% 41% 6%	27 Gy/2 n=96 G2 20% 5% 4% 1%	G3 3% 4% 0% 1%	P value .31 .22 .001 .62 .57 .18
Table 3 Chronic tox  Toxicity  Frequency/urgency Dysuria Retention Incontinence Hematuria	G1 35% 18% 19% 7% 6%	on dosing s 38 Gy/4 n=319 G2 19% 8% 5% 2% 7%	G3 1% 1% 2% 0.8% 0.8%	G1 37% 20% 17% 13% 4%	(N=494) 24 Gy/2 n=79 G2 23% 3% 0% 3% 4%	G3 0% 0% 0% 0% 0%	G1 44% 24% 41% 6% 4%	27 Gy/2 n=96 G2 20% 5% 4% 1% 11%	G3 3% 4% 0% 1% 0%	P value 31 .22 .001 .62 .57 .18 .70
Toxicity  Toxicity  Frequency/argency Dysuria Retention Incontinence Hematuria Diarrhea	G1 35% 18% 19% 7% 6% 6%	on dosing s 38 Gy/4 n=319 G2 19% 8% 5% 2% 7% 1%	G3 1% 1% 2% 0.8% 0.8% 0%	GI 37% 20% 17% 13% 4% 12%	(N=494) 24 Gy/2 n=79 G2 23% 3% 0% 3% 4% 1%	G3 0% 0% 0% 0% 0% 0%	G1 44% 24% 41% 6% 4% 13%	27 Gy/2 n=96 G2 20% 5% 4% 11% 0%	G3 3% 4% 0% 1% 0%	P value .31 .22 .001 .62 .57 .18



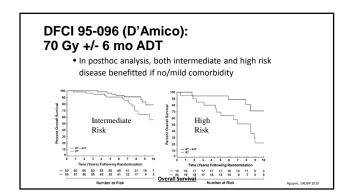


### NCCN Unfavorable Intermediate Risk Generally adds short-course ADT to radiation

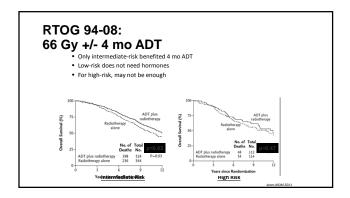
- RF
- EBRT + 4 to 6 months ADT
- EBRT + Brachy Boost (+/- 4 to 6 months ADT)

# ADT Potentiates Radiation Damage by Blocking DNA Damage Repair RESEARCH ARTICLE A Hormone–DNA Repair Circuit Governs the Response to Genotoxic Insult Jonatha F. Goodwin, Matthew J. Schlewer, Jeffry L. Dawn, Tang MA, Robert B. Den't, Adden P. Dickart<sup>1</sup>. Felix Y. Fang<sup>1,6,7</sup>, and Karen E. Knudsen<sup>1,2,8,4</sup> Felix Y. Fang<sup>1,6,7</sup>, and Karen E. Knudsen<sup>1,2,8,4</sup> Cancer Discover 2013 Cancer Discover 2013 Cancer Discover 2013

## 



# RTOG 94-08: 66 Gy +/- 4 mo ADT • 1,979 men w/ T1b-T2b, and PSA < 20 • 35% low, 54% intermediate; 11% high risk • Improvement in overall survival with ADT A All Patients A DT plan reduction provided by a long state of the patients of th



## The Trials Used Lower Doses Than Current Standard (>75Gy)

Trial	Dose (Gy)
DFCI	70 Gy
RTOG	66 Gy
TROG	66 Gy

 Is short-course ADT needed for men with intermediate risk prostate cancer treated with doseescalated (> 75 Gy) radiation?

# Need for ADT with Dose-Escalated EBRT is Being Studied in RTOG 0815



# EORTC Trial Suggests ADT Still Benefits w/Dose Escalated RT

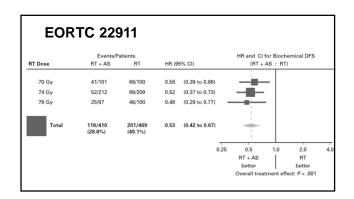
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Short Androgen Suppression and Radiation Dose Escalation for Intermediate- and High-Risk Localized Prostate Cancer: Results of EORTC Trial 22991

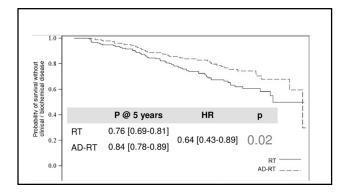
Model Bell, Philips Assigns, Crimina Carris, Subander Villa, Perco Kinia, Philip M.P. Poermans, Sandhaum Sundar, Elbeita M. vas der Store, Banull, John Armstrong, Jan-François Boux, Fernanda Cherten, Bandy Erich, Noorde Mar, André Bell, Balaman Ben Del, Del Robelma, France College, Lancer Roual, Eand Stad. Centrel Cons. Aplanna CM: van der Bergh, and Lancer College.

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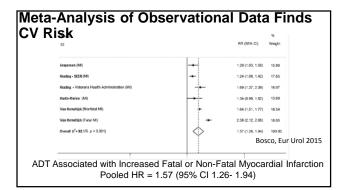


# GETUG-14 Confirms that ADT needed w/80Gy

- 377 men w/intermediate risk prostate CA
- 80Gy RT vs. 80Gy RT+ 4 months of ADT
- RT=Prostate+SV to 46Gy, Prostate to 80Gy



### What about cardiac harms of ADT?



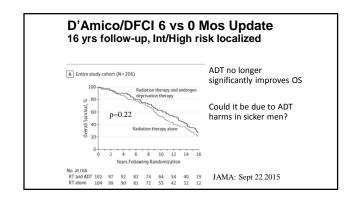
### Meta-Analysis of Randomized Data Finds Relative Risk (95% CI) 1.30 (0.71-2.38) EORTC 22863 (Bolla) DFCI 95-096 (D'Amico) 1.02 (0.50-2.09) TROG 96.01 (Denham) 0.79 (0.48-1.31) 0.79 (0.56-1.11) 3.26 (0.35-30.2) RTOG 85-31 (Efstathiou) .17 ECOG EST-3886 (Messing) RTOG 86-10 (Roach) 1.24 (0.76-2.01) EORTC 30846 (Schroder) EORTC 30891 (Studer) 0.91 (0.70-1.18) Overall (fixed-effects model) 0.93 (0.79-1.10) Test for heterogeneity: Q=5.12, p=.645, I-squared=0.0% Nguyen, JAMA 2011 ADT Not Associated with Increased Fatal Myocardial Infarction

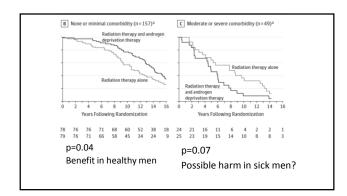
Pooled HR = 0.93 (95% CI 0.79- 1.10)

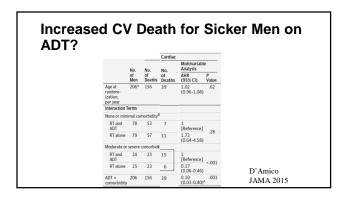
# What Could Explain Discrepancy Between Randomized and Observational Data?

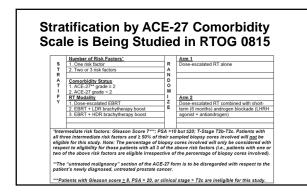
- 1) The results from observational data reflect confounding (e.g. sicker pts get ADT)
- 2) The observational results included non-fatal MIs while randomized only looked CV Death
- Perhaps ADT causes harm mainly in men with pre-existing comorbidities, who are underrepresented in randomized trials

Is there a subgroup of men who could be harmed by ADT?



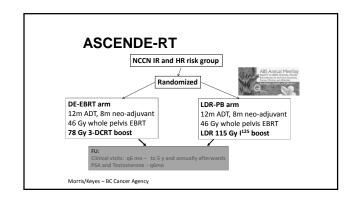


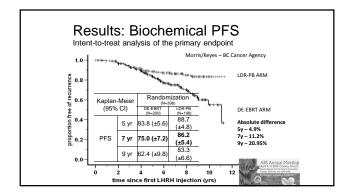


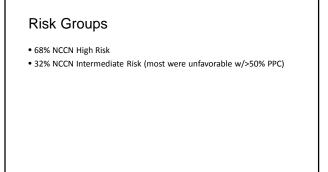


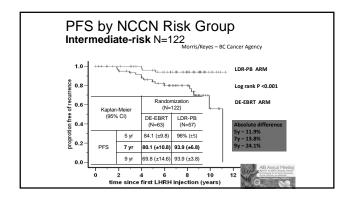
# My Recommendations for ADT and CV Risk: Continue to use short-course ADT for patients w/unfavorable intermediate risk disease For favorable intermediate, rates of recurrence are low, and dose escalated radiation alone without ADT is reasonable for select cases For unfavorable risk w/multiple comorbidities, a post-hoc analysis suggests they may not benefit from ADT, but until RTOG 08-15 is published, these patients should still receive ADT and should be medically optimized w/a cardiologist, monitored closely for diabetes and hyperlipidemia and encouraged to exercise.

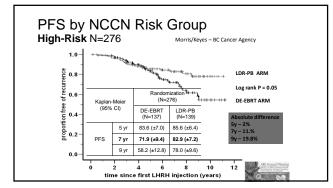
Role of Brachytherapy Boost:
ASCENDE-RT











# ASCENDE-RT Considerations For Int Risk

Large Absolute Benefit in men with Intermediate Risk Disease (Mostly Unfavorable Intermediate): 94% vs. 70% PFS at 9 years

Increase in Urethral Strictures with Boost: 8% vs. 2%

No difference in survival yet

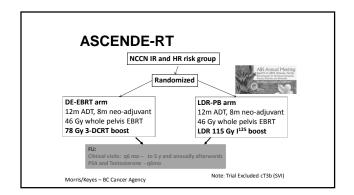
Worthwhile for younger, healthy men, with unfavorable intermediate risk disease

### NCCN Unfavorable Intermediate Risk Generally adds short-course ADT to radiation

- RP
- EBRT + 4 to 6 months ADT
- EBRT + Brachy Boost (+/- 4 to 6 months ADT)

### NCCN High Risk Adds Long-course ADT to radiation

- RF
- EBRT + 2 to 3 years ADT
- EBRT + Brachy Boost + 1 to 3 years ADT
  - Note: 1 year duration was used in ASCENDE-RT trial, but the efficacy of this specific duration was never tested



What is the Optimal Duration of ADT?

Localized		d	Locally- Advanced	Node Positive
Low Risk	Interm Risk	High Risk		
	DFCI	95-096	EORTC	RTOG 85-31
	6 m	onths	36 months	Lifelong
	RTOG	94-08	*RTOG 92-02	
	4 m	onths	DART 01/05	
			28 months	
		TR	OG 96.01	
		6	months	
		TROG 0	3*04 (RADAR)	
		18	months	

### **Summary: ADT Durations with RT**

	Localized			Locally- Advanced	Node Positive
	Low Risk	Interm Risk	High Risk		
Stand ard	*	4 mos		8-36 mos	Lifelong
?			18	3 mos	2-3 yrs

NCCN Recommendation: Long-Course ADT (2-3 years) for High Risk to Locally Advanced Disease

### RTOG 92-02 Horwitz (JCO 2008)

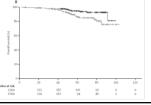
- cT2C T4 and PSA < 150 (55% T3/4)
- 1554 pts. 65-70Gy + 4 vs. 28 mos ADT

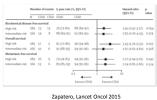
28 mos improved 10-yr PC-specific survival (89 vs. 84%, p=0.0042)

OS improved only in a post-hoc analysis of Gleason 8-10 subgroup (45 vs. 32% p=0.0061)

### DART 01/05 Trial (Lancet Oncol 2015) Redid RTOG 92-02 Using High Dose (78Gy) RT

• Essentially Same Results (28 mos improves OS Compared to 4 mos). No proven OS benefit in Intermediate Risk





### **EORTC Bolla (NEJM 2009)**

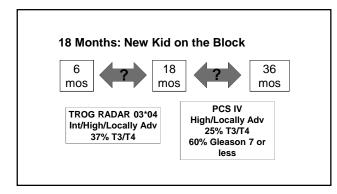
- 77% T3 or T4, 6.3% N1
- 970 pts. 70Gy + 6 vs. 36 mos ADT

36 mos reduced 5-yr overall mortality by 3.8% (15.2% vs. 19.0%)

### **Long-Term ADT**

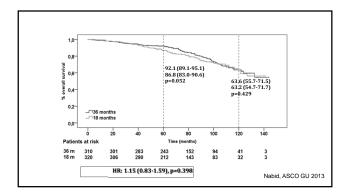
Based on the EORTC, RTOG, and DART trials, 2-3 years of ADT is considered the current standard of care for high risk/locally advanced patients

But what about 18 months?



### **PCS IV Nabid ASCO GU 2013**

- Patients: 630 High Risk/Locally Adv
- Incl. criteria: T3/4 (25%) or PSA>20 (44%) or GI 8-10 (40%)
- 70 Gy + 18 vs 36 months of ADT
  - Median f/u 77 months
- Biochem failure 25 vs. 19.4% (p=0.08)
- No signif difference in OS (HR 1.15, p=0.398)



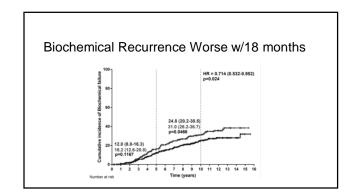
### Problems with 18 months in 2013

- PCS IV was not powered as an equivalence or non-inferiority study
- 18 months not proven to be equivalent or non-inferior to the standard 36 mos HR=1.15 (0.83-1.59) upper bound of 1.59 was too high to say non-inferior
- Needed more follow-up

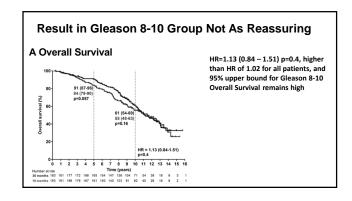
### ASCO 2017 Updates, Nabid et al

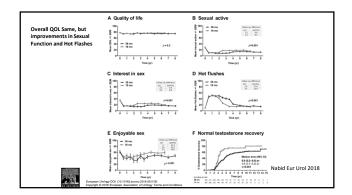
	ASCO GU 2013	ASCO 2017
Median f/u	6.4 years	9.4 years
Deaths	147	290
HR for All-Cause Mortality	1.15 [0.83-1.59]	1.02 [0.81-1.29]

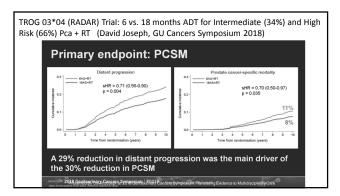
- Is an upper limit of 1.29 good enough?
  - Bolla NEJM 2009: 36 vs. 6 mos pre-set a 1.35 upper limit
  - Crook NEJM 2012: intermittent vs. continuous set a 1.25 upper limit



# Compliance Was Poor in the 36 Month Arm • 25% in the 36 month arm received 18 months or less, & only 59% received 36 months, which biases towards a null result.

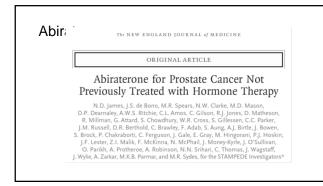


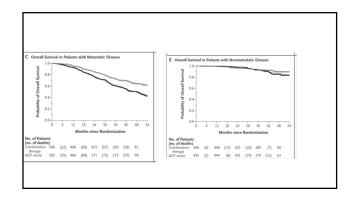


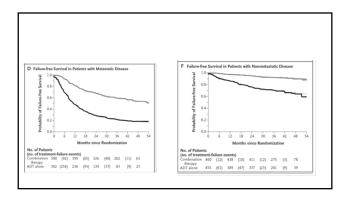


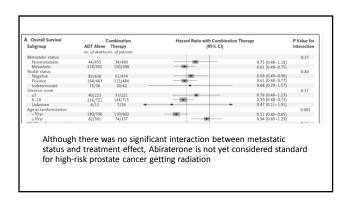
### **Summary: ADT Durations with RT** Localized Locally-Node Advanced Positive Low Interm High Risk Risk Risk Standar 4 mos 28-36 mos Lifelong d 6 mos ? 18 mos 2-3 yrs

# Additional Agents in the High-Risk Space? • Docetaxel (Sandler) • RTOG 05-21: 4% improvement in OS at 4 years, but 2-sided p-value was 0.08 (1-sided=0.04) so not yet accepted widely • Enzalutamide (Williams, Nguyen, Sweeney) • ENZARAD closed to accrual • Apalutamide (Sandler) • ATLAS closed to accrual • Abiraterone (James) • Reported

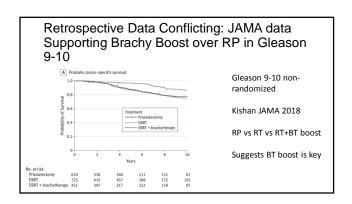






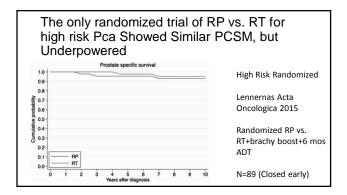


How do Radiation and Surgery Compare for High Risk Disease?



### Retrospective Data Conflicting: Eur Urol Systematic Review of Retro Data Supporting RP over RT

- Wallis, et al Eur Urol 2016
- Systematic Review and Meta-Analysis of Observational Data
- HR for Overall Mortality RT vs. RP: 1.63 (1.54-1.73), p<0.00001
- HR for PC-Mortality RT vs. RP: 2.08 (1.76 2.47) p<0.00001



### Summary: NCCN High Risk Adds Long-course ADT to radiation

- RF
- EBRT + 2 to 3 years ADT
- EBRT + Brachy Boost + 1 to 3 years ADT
  - Note: 1 year duration was used in ASCENDE-RT trial, but the efficacy of this specific duration was pover tested.

Post-Operative Adjuvant and Salvage RT

### ASTRO/AUA Guidelines

- Recommend Discussing and Potentially Offering Adjuvant Radiation to all patients with either:
  - Positive Margin
  - Pathologic T3 or higher Disease
- In current practice, fewer than 10% of patients with these features receive adjuvant RT nationwide.

## 3 RCTs Suggest Adjuvant RT Improves bRFS, But only 1 Showed OS Benefit

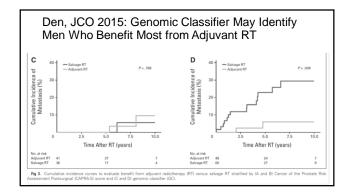
	Inclusion Criteria	%PSA<0.2 at entry	f/u yrs	HR for bRFS	OS Benefit
SWOG 8794 Thompson	pT3 or +margin	66%	12.6	0.43	YES
EORTC 22911 Bolla	pT3 or +margin	70%	10.3	0.48	No
ARO 96-02 Wiegel	pT3	100%	9.2	0.53	No

Adjuvant RT cuts the risk of PSA recurrence by about 50%

# **SWOG Trial: Only Trial that Showed** Adjuvant RT Improved OS But, only 32% in control arm got salvage RT, and it was initiated too late (when PSA =1.0 median), and 33% had detectable PSA at Entry Not a Trial of Adjuvant vs. Modern Day Close Observation with Early salvage

### **Long-Term Toxicity Tolerable**

	Incontinence	Stricture	Rectal
SWOG 8794 "Thompson"	6% vs 3% (p=0.11)	18% vs 9% (p=0.02)	3.3% vs. 0% (p=0.02)
EORTC 22911 "Bolla"	23% vs 17% (p=NS) (any leakage)	NR	NR
ARO 96-02 "German"	Not assessed	1 in each arm	1.4% vs 0%



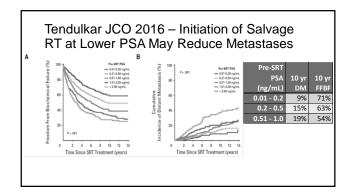
### Risk-Adapted Approach May be Most Sensible

- $\bullet$  I consider adjuvant for young patients with the highest absolute risk of recurrence, as they will have the highest absolute benefit from a 50% relative reduction in recurrence
- Note that 40% with pT3 or positive margin remain disease-free on observation alone through 10 years (Bolla EORTC Trial)
- Genomic Testing May also Help Identify Patients who Benefit Most from Adjuvant RT

### RADICALS, RAVES, and EORTC Trial Seek to Answer the Adjuvant vs. Early Salvage Question

- RADICALS:
  - 2x2 Trial of Adjuvant vs. Early Salvage Radiation at PSA >0.2
- And 0 vs. 6 vs. 24 months of ADT
- RAVES:
  - Adjuvant vs. Early Salvage Radiation at PSA >0.2
- EORTC:
  - Adjuvant vs. Early Salvage Radiation at PSA >0.1

Salvage RT + ADT



### RTOG 96-01: Survival Benefit to Adding ADT to Salvage RT 13-year follow-up

- Rising PSA after RP (pT3 or pT2R1), N=771
  - Median PSA at entry was 0.6
- Salvage RT +/- 2 years bicalutamide 150mg

10-year	RT	RT+ADT	HR	P-value
Metastasis	19%	11%	0.63	P<0.01
PCSM	10.1%	4.5%	0.49	P<0.001
OS	78%	82%	0.77	P=0.036

GU Cancers Symposium, 2016 NEJM, 2017

### The Case for ADT Today

- Proven Overall Survival Benefit
- Reasonable number needed to treat ratios

Outcome	Absolute Benefit at 10 years	Number Needed to Treat
Metastasis	8%	12
PCSM	5.6%	18
Overall Mortality	4%	25

### GETUG/AFU-16 - No survival benefit (yet)

- N=743
- Rising PSA after RP
- Salvage RT +/- 6 mos goserelin

5-year	RT	RT+ADT	
bRFS	62.1%	79.6%	P<0.001
OS	94.8%	96.2%	P=0.18

Lancet Oncology, 2017

### Why 6 months GnRH agonist may be Enough

	RTOG 96-01	GETUG-16
	2 yrs bicalutamide	6 mos goserelin
brfs hr	0.48 (p<0.001)	0.50 (p<0.0001)
OS HR	0.77 (p=0.04)	0.70 (p=0.18)
Median FU	13 years	5 years

### Case Against ADT: Subgroup Analyses

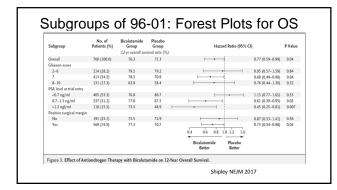
PSA <0.7: No benefit to ADT

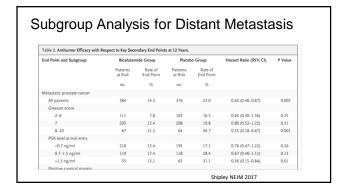
PSA 0.7-1.5: Moderate benefit to ADT

PSA >1.5: Larger Benefit to ADT

Don't most patients getting salvage XRT today have a PSA less than 0.7??

Note this 0.7 cutoff was not pre-stratified (Only PSA >1.5 was pre-stratified)

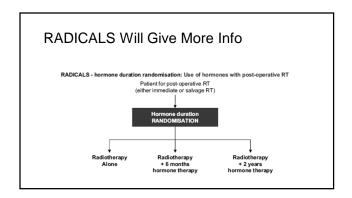




# Which patients can avoid ADT?

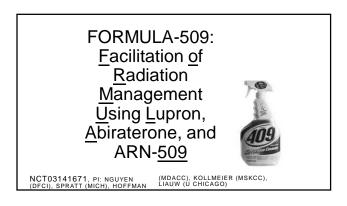
The PSA <0.7 was an unplanned subgroup analysis, so cannot have complete confidence in this, but...

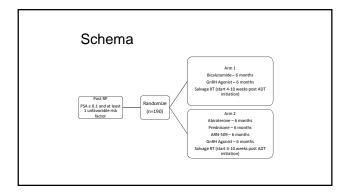
For PSA<0.5 w/positive margins, Gleason<= 3+4=7, pT2, absolute benefit of ADT on OS likely small, especially if older



### NRG GU-006 (PI – Dan Spratt)

- Randomized Phase II Trial Focused on Patients with more favorable risk getting salvage radiation
  - Biomarker Stratified by PAM 50
  - Randomized to Radiation vs. Radiation + Apalutamide
- NCT03371719

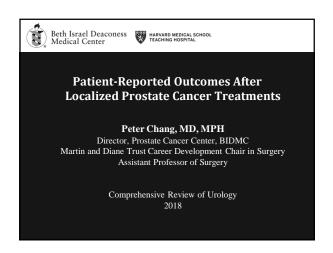


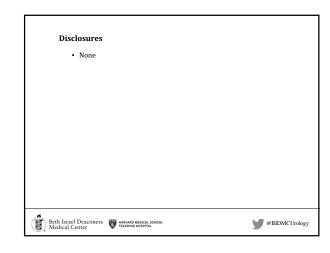


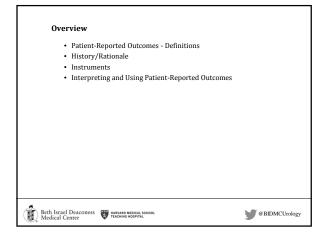
### **Summary Post-Op**

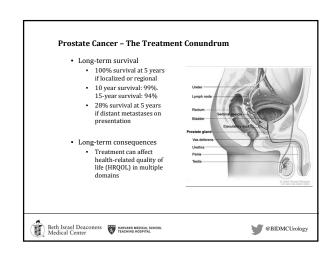
- Risk-Adapted Consideration of Adjuvant RT for Young Margin Positive or pT3 Patients with Highest Absolute Risk of Recurrence
- For Most Others, Close Observation and Early Initiation of Salvage Radiation when PSA Rises to 0.1 or 0.2 May Yield Similar Survival and Spare 40% of Men from Radiation
- Salvage Radiation Typically Should be Accompanied by 6 months of GnRHbased ADT (or less commonly 2 yrs bicalutamide)
- Some controversy as to whether patients with PSA <0.7 at salvage have enough benefit from ADT with salvage RT

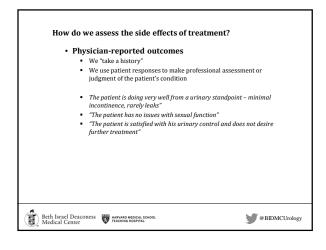
Thank you!

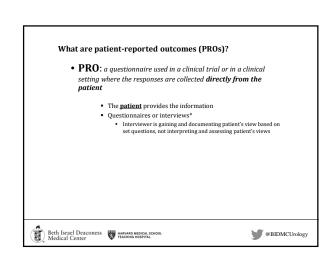




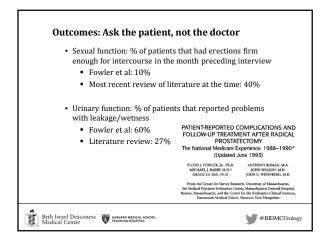


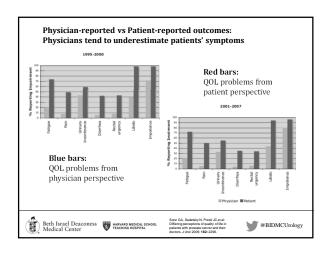


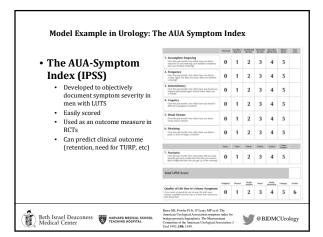


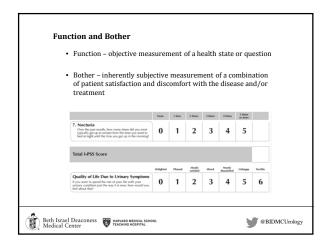


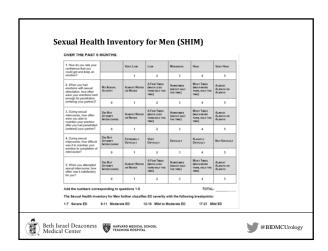
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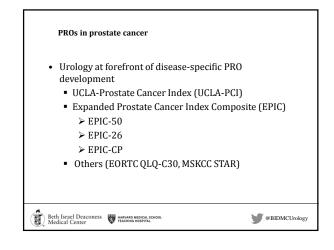












### UCLA-Prostate Cancer Index (UCLA-PCI)

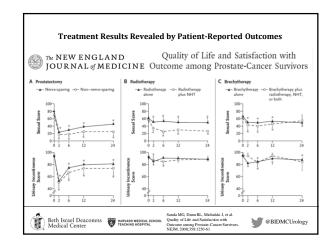
- Developed by Mark Litwin et al in 1995
- Construct validity are the questions relevant and representative of the construct (prostate cancer)?
- Multi-step, iterative process
  - · Patient focus groups
  - Psychometric assessment and validation
- · Identified health domains affected by prostate cancer treatment
- Measured function and bother

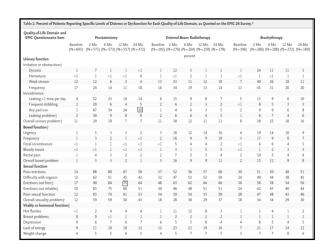
Urinary (incontinence)	Sexual	Bowel
Function (5)	Function (8)	Function (4)
Bother (1)	Bother (1)	Bother (1)

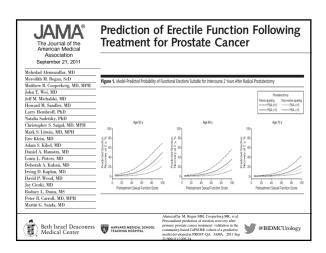


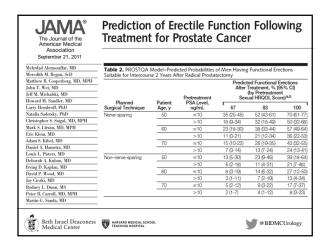
# Expanded Prostate Cancer Index Composite Developed by Wei and Sanda et al in 2000 Health Domain Expansion to capture effects of a broader array of treatments (brachytherapy, hormonal therapy) Urinary incontinence Urinary irritation/obstruction Bowel Sexual Vitality/Hormonal So items total Rept bother items from UCLA-PCI

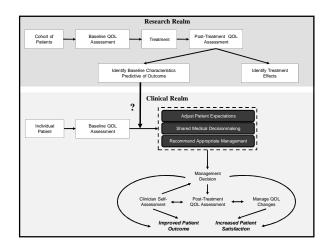


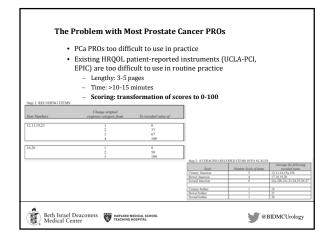


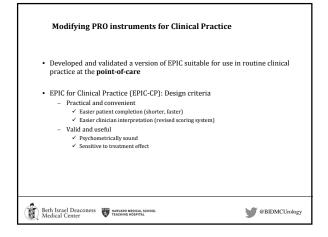


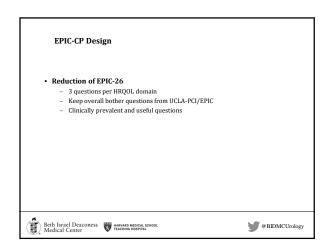


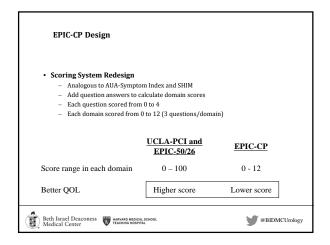


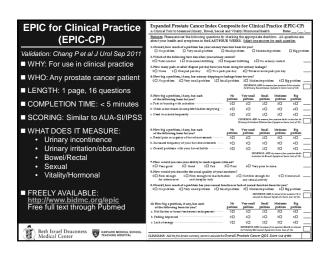










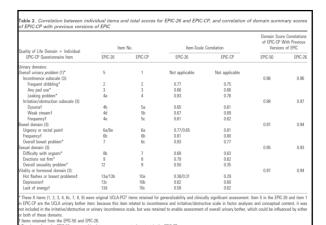


Expanded Prostate Cancer Index Composite for Clinical Practice: Development and Validation of a Practical Health Related Quality of Life Instrument for Use in the Routine Clinical Care of Patients With Prostate Cancer

Peter Chang, Konrad M. Szymanski, Rodney L. Dunn, Jonathan J. Chipman, Mark S. Litwin, Paul L. Nguyen, Christopher J. Sweeney, Robert Cook, Andrew A. Wagner, William C. DeWolf, Glenn J. Bubley, Renee Funches, Joseph A. Aronovitz. John T. Wei\* and Martin G. Sanda\*†,‡

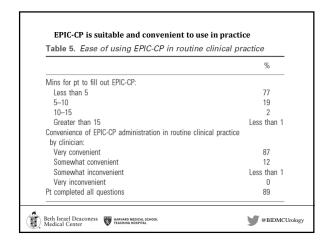
- Psychometrically sound (Cronbach's alpha > 0.70)
- All domains correlate highly (>0.9) with EPIC-26/50
- · Sensitive to treatment effects
- · Practical for clinical practice
  - \* 77% of patients completed in < 5 min, 96% in <10 min
  - 87% of clinicians found EPIC-CP very convenient to use in the flow of routine clinical practice





### 

### EPIC-CP is sensitive to treatment effects on HRQOL Table 4. Sensitivity of the EPIC-CP to HRQOL differences associated with prostate cancer treatment Active All Anv HRQOL Domain\* Surveillance Untreated p Valuet Treatment No. pts 175 Mean urinary (SD): Overall urinary bother 1.32 (1.29) 1.25 (1.32) 1.11 (1.17) Incontinence 1.76 (2.27) 0.87 (1.41) 1.06 (1.85) 0.004 Irritation/obstruction 2.79 (2.62) 2.28 (2.22) 2.16 (1.99) 0.02 1.65 (2.48) 0.94 (1.63) 1.11 (1.88) 0.04 Mean bowel (SD) Mean sexual (SD) 6.47 (3.92) 4.16 (3.12) 3.73 (3.20) < 0.0001 Mean vitality/hormonal (SD) 2.43 (2.57) 1.88 (2.14) 1.92 (2.38) 0.08 Overall scores 14.66 (9.00) 9.77 (7.40) 9.59 (7.75) < 0.0001 Beth Israel Deaconess Medical Center Beth Israel Deaconess Medical Center @BIDMCUrology



## Measuring and Predicting Prostate Cancer Related Quality of Life Changes Using EPIC for Clinical Practice

Jonathan J. Chipman, Martin G. Sanda, Rodney L. Dunn, John T. Wei, Mark S. Litwin, Catrina M. Crociani, Meredith M. Regan, Peter Chang\* and the PROST-QA Consortium

- Further validation and characterization of EPIC-CP using the PROST-QA cohort
- Objectives:
  - Assess the ability of EPIC-CP to detect treatment-related changes over time
  - Apply EPIC-CP to render an existing multivariable PROST-QA predictive model usable at the point of care
  - Determine what constitutes a clinically meaningful change in EPIC-26 and EPIC-CP score



# EPIC-CP: Responsive to HRQOL changes over time Table 2. Domain specific short-term and long-term changes in EPIC-CP accords from preferational to the property of the propert

### EPIC-CP: Defining the MID

- · Domain summary scores can be difficult to interpret
- What change in score is clinically relevant?
- · "Minimally important difference
- · Also called "clinically significant change"
- · Distribution and anchor-based approaches

### Table 3. EPIC-CP minimally important differences

	MID (treatment group range
Urinary incontinence	1.0 (0.7—1.5)
Urinary irritation/obstruction	1.3 (1.1—1.4)
Bowel	1.2 (0.9—1.5)
Sexual	1.6 (1.4—1.9)
Vitality/hormonal	1.0 (0.9—1.3)
Vitality/hormonal	1.0 (0.9—1.3)
Beth Israel Deaconess HARVARD MEDICAL SCHOOL	@BIDMCUre

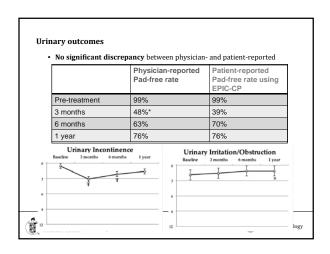
Ann In	Age (ng/dl		EPIC-CP Score*,† EPIC-26 Sco		C-26 Score	ore*,6	
pretreatme		0	2	4	100	83	67
			Nerve sp.	aring			
50:		07	20	0.4	70	20	0.5
10 or Le Greater		67 46	30 50	34 18	70 50	32 52	35 18
60:	triali 10	40	30	10	30	52	10
10 or Le	ss	53	36	22	57	38	23
Greater		32	19	11	36	21	11
70:							
10 or Le		39	24	14	43	26	15
Greater	than 10	21	12	6	24	13	7
		1	Nonnerve s	sparing			
50: 10 or Le		0.5	21	12	20	20	13
TU or Le		35 19	10	6	39 21	23 11	13
60:	triali 10	19	10	0	21	- 11	0
10 or Le	22	23	13	7	27	15	8
Greater		11	6	3	13	7	3
70:							
10 or Le		15	8	4	17	9	5
Greater	than 10	7	3	2	8	4	2

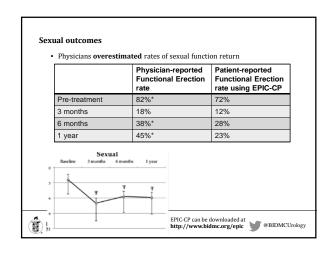
### How does EPIC-CP perform in the real-world?

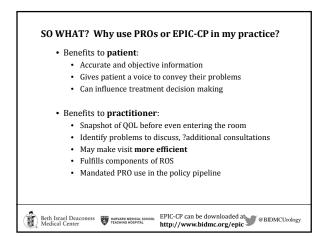
- Is it FEASIBLE to use outside of research? Is there a discrepancy between patient-reported and physician-reported outcomes?
- 482 Robotic Prostatectomy patients at BIDMC from 2010 to 2014
- EPIC-CP Questionnaires used in routine practice to assess QOL
  - · No research personnel involved in administration
  - · Given at baseline and at every follow-up visit after surgery
  - Prospective administration (Point of care in clinic)
- Reviewed demographic and QOL results
- 708 EPIC-CP questionnaires reviewed at time of submission

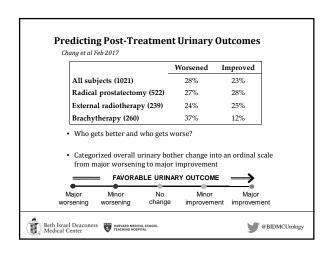


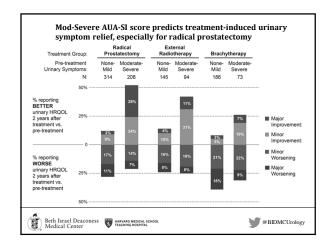
# Clinical Use of Expanded Prostate Cancer Index Composite for Clinical Practice to Assess Patient Reported Prostate Cancer Quality of Life Following Robot-Assisted Radical Prostatectomy Andrew A. Wagner, \* Philip J. Cheng, \* Arie Carneiro, Ostap Dovirak, Arjun Khosla, Kimberly N. Taylor, Catrina M. Crociani, Kyle C. McAnally, Andrew Percy, Lauren E. Dewey, Martin G. Sanda and Peter Chang† Table 1. Characteristics of 482 patients 1. Age greater than 80 1

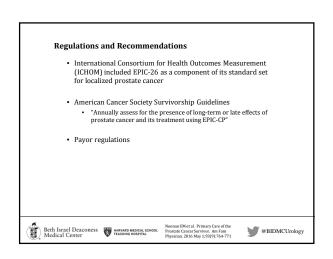


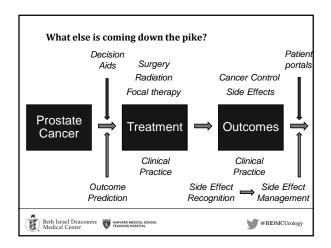


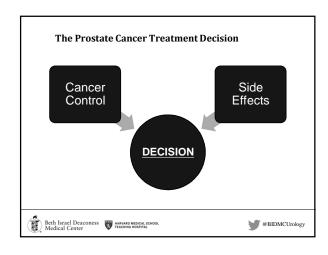


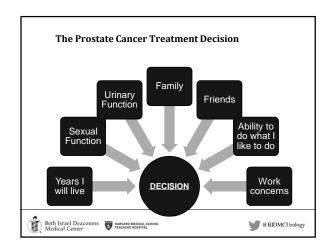


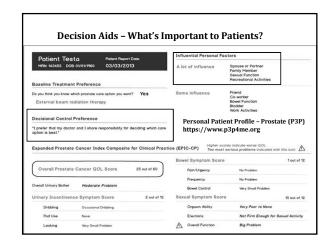


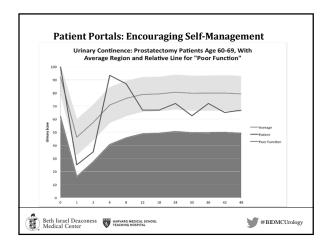


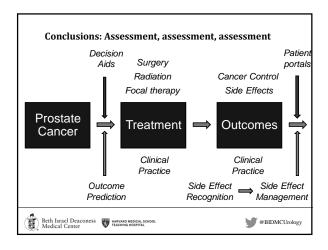


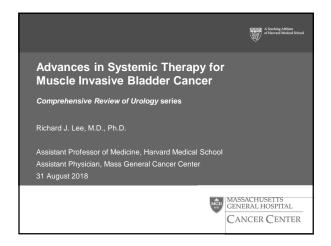


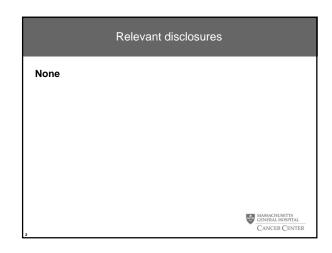




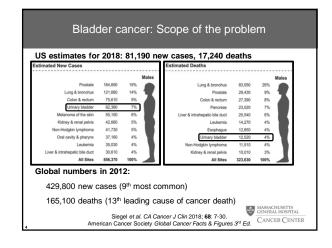






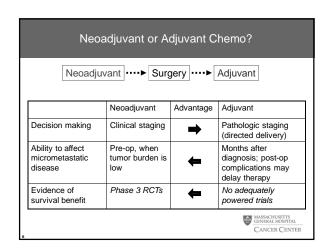


# Objectives Bladder cancer To understand the role of peri-operative chemo To understand the regimens in common use To consider future targets for therapy

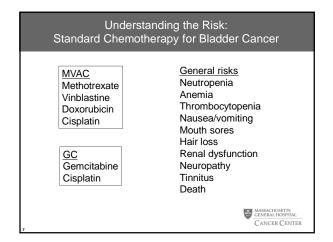


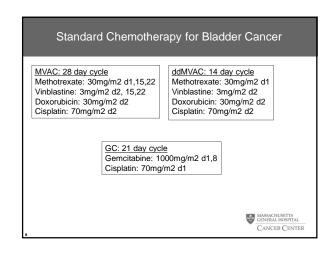
Pros/cons of neoadjuvant and adjuvant chemotherapy
Current standard chemotherapy regimens
Evidence for adjuvant chemotherapy
Evidence for neoadjuvant chemotherapy
A look into the future

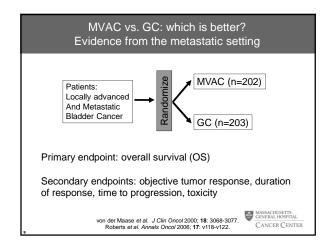
The #1 goal of peri-operative chemotherapy:
Improve cure rates.

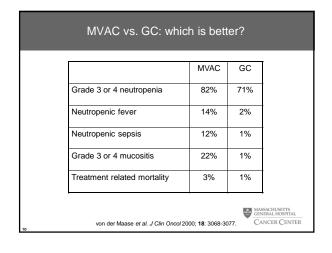


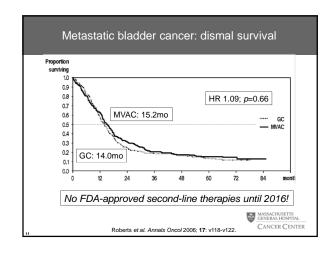
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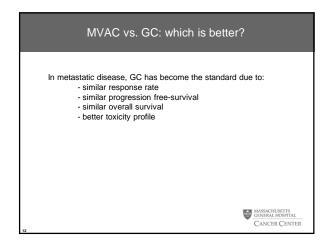


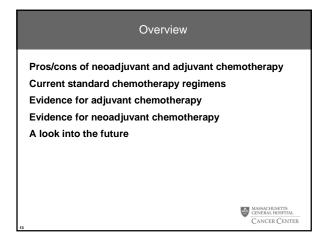


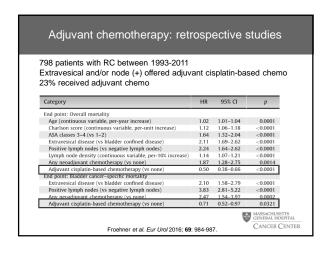




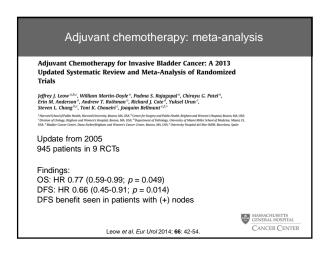


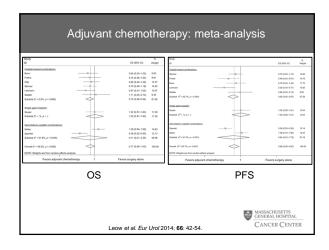


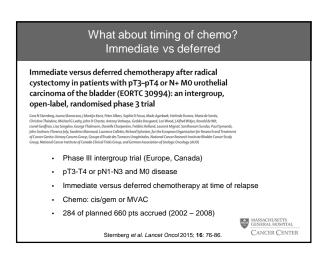


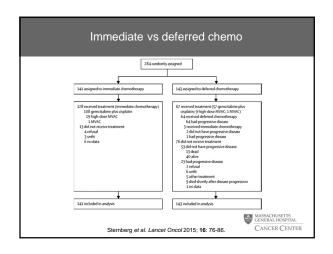


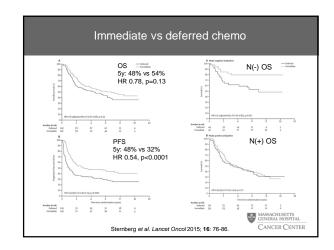
### Adjuvant chemotherapy for bladder cancer: Reported RCTs Institution Regimen Survival Completed benefit accrual USC 91 Cis/dox MVAC/MVEC U of Mainz, Germany 49 Yes Yes Swiss Gp for Clin Can Res 77 Cisplatin No Yes CMV Stanford 55 Nο Yes US Intergroup 114 MVAC Nο Nο Italian multicenter 194 GC No No SOGUG (Spain) 142 PCG Yes No Skinner et al. J Urol 1991; 145: 459-464. Stockle et al. J Urol 1995; 153: 47-52. Studer et al. J Urol 1994; 152: 82-84. Freiha et al. J Urol 1996; 155: 495-499. Stadler et al. J Clin Oncol 2011; 29: 3443-3449. Cognetti et al. Ann Oncol 2012; 23: 695-700. Paz-Ares et al. J Clin Oncol 2010; 28 (Suppl): 18s. CANCER CENTER





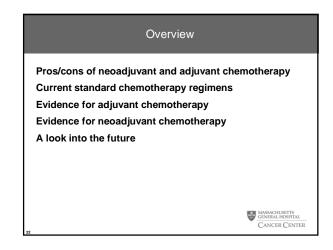




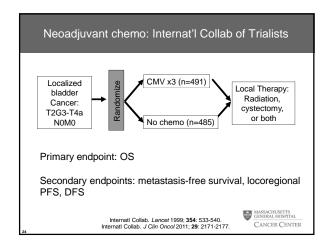


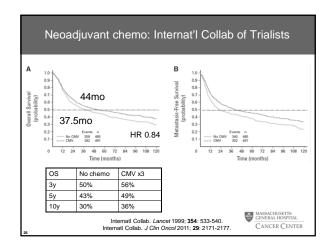
# Adjuvant chemotherapy for bladder cancer No definitive prospective data support adjuvant chemotherapy - underpowered studies - failure to complete accrual - meta-analyses: suggestive of benefit Do we give it? In practice, adjuvant chemo is often given to patients with node-positive and/or extra-vesical disease who can tolerate chemo

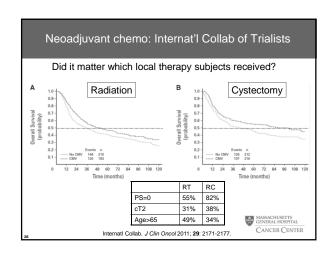
MASSACHUSETTS
GENERAL HOSPITAL
CANCER CENTER

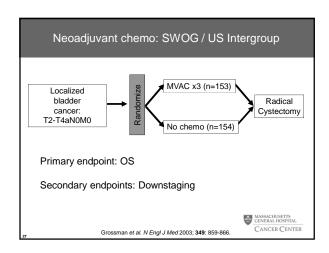


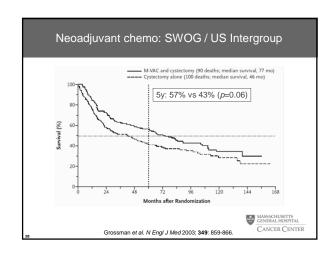
Trial	N	Eligibility	Regimen	Survival Benefit	Comment	
Nordic Cystectomy I	325	T1G3-T4a NxM0	(Cisplatin + doxorubicin) x2	No	Nonconventiona chemo regimen neoadjuvant RT	
Nordic Cystectomy II	317	T2-T4a NxM0	(Cisplatin + methotrexate) x3	No	Nonconventiona chemo regimen	
Internat'l Collab of Trialists	976	T2G3-T4a N0M0	CMV x3	Yes	Local therapy: RT, RC, RT+RC	
SWOG/US Intergroup	317	T2-T4 N0M0	MVAC x3	Yes		

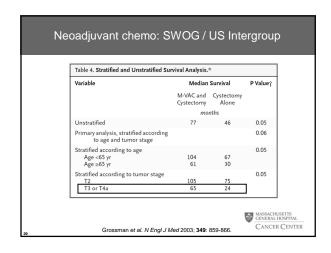


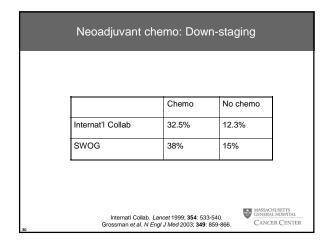


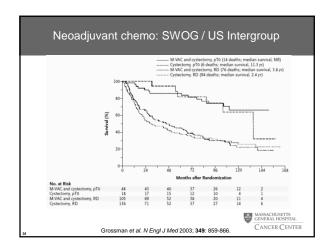


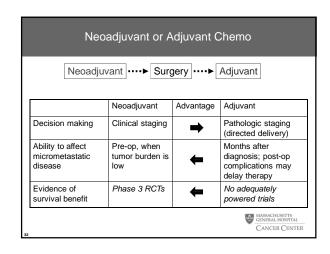


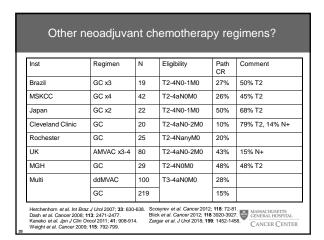


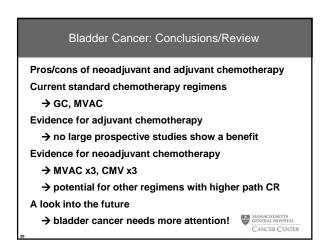


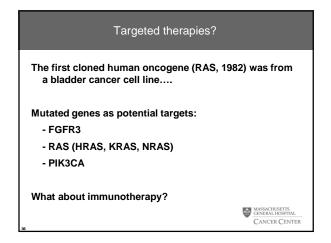


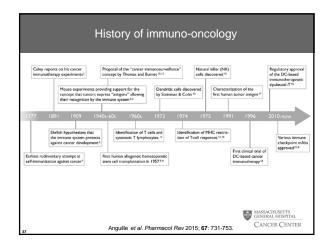


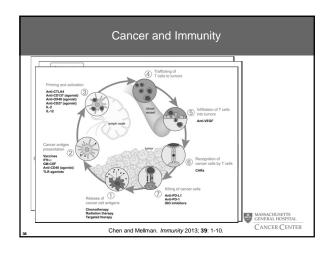


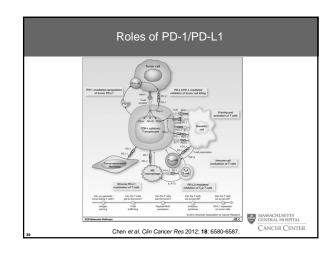


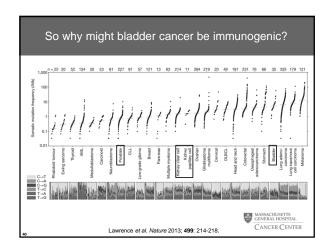


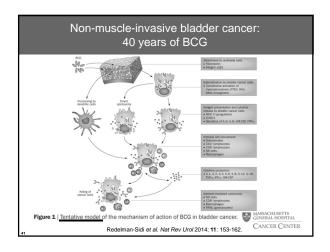


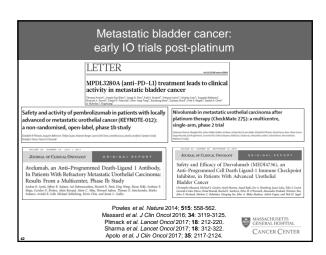


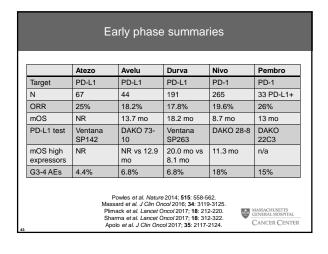


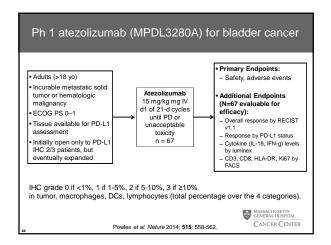




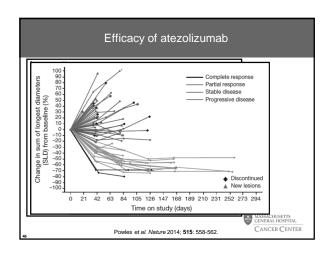


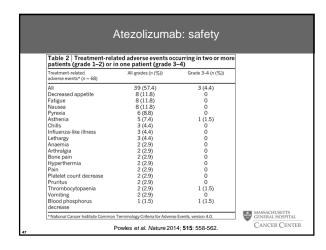


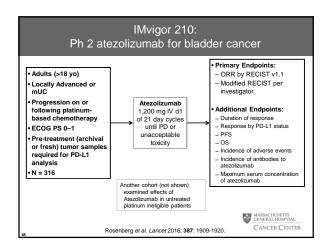


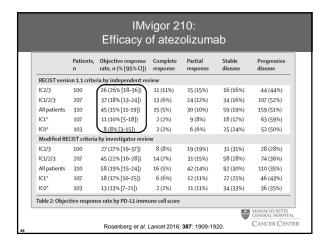


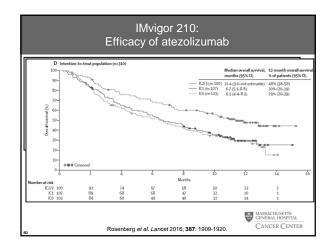
Tumour-infiltrating immune cells and objective response rates						
	Objective response rate n (%)	Stable disease n (%)	Progressive disease n (%)			
IHC 2/3 (n = 30)	13 (43.3) (95% Cl: 25.5–62.6)	8 (26.7)	8 (26.7)			
IHC 3 (n = 10)	5 (50.0) (95% Cl: 22.2–77.8)	2 (20.0)	3 (30.0)			
IHC 2 (n = 20)	8 (40.0) (95% CI: 20.9–63.9)	6 (30.0)	5 (25.0)			
IHC 0/1 (n = 35)	4 (11.4) (95% CI: 4.0–26.3)	13 (37.1)	13 (37.1)			
IHC 1 (n = 23)	3 (13.0) (95% CI: 3.7–31.7)	8 (34.8)	8 (34.8)			
IHC 0 (n = 12)	1 (8.3) (95% CI: 0.4–34.9)	5 (41.7)	5 (41.7)			

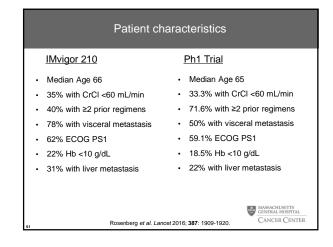


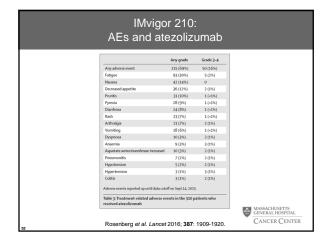


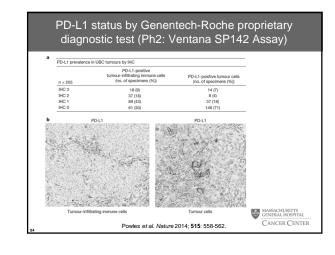


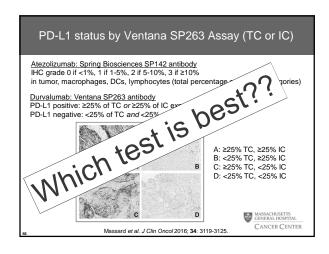


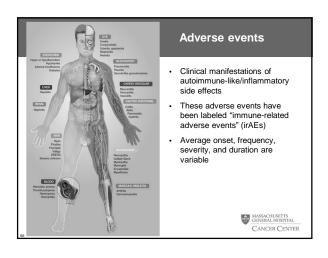


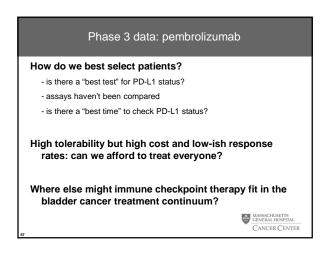


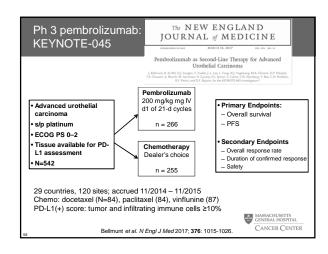


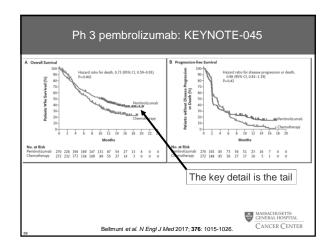


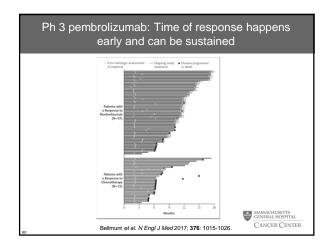


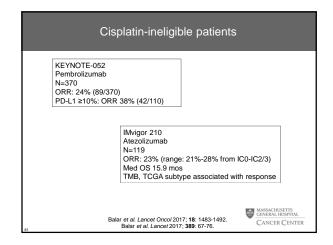


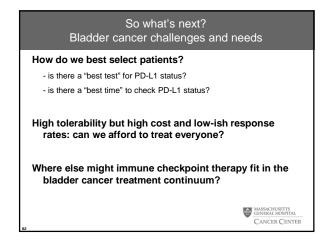


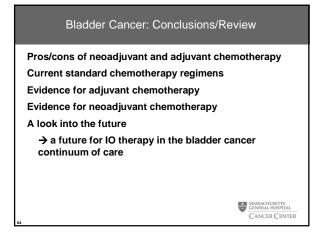


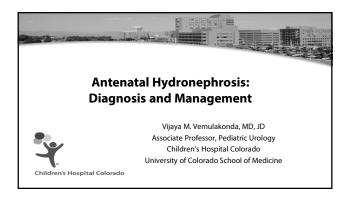


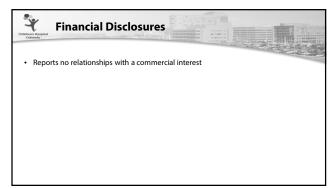


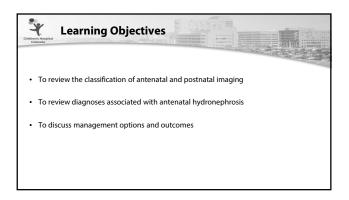


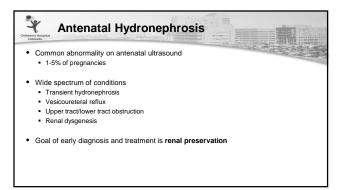


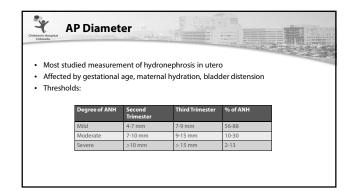




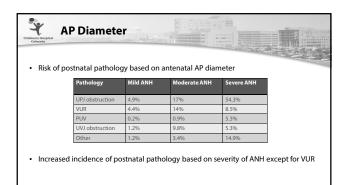


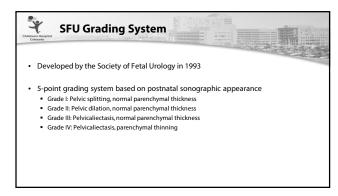


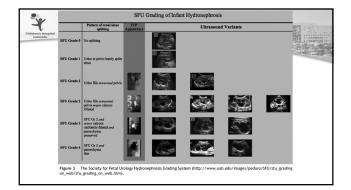


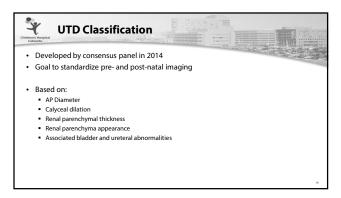


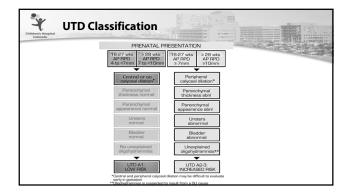


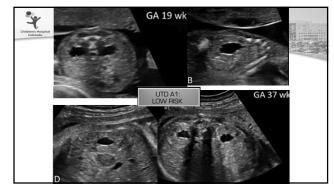


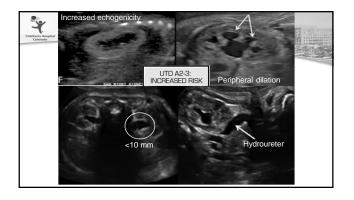


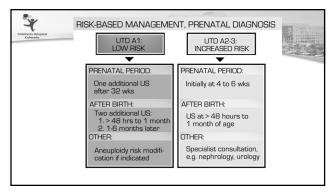


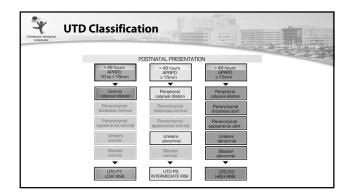


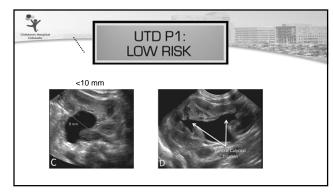


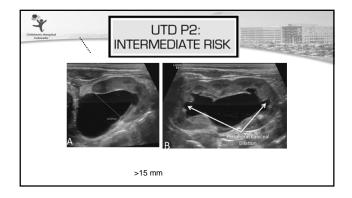


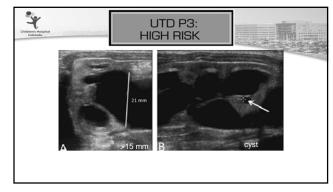


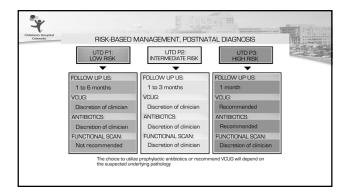


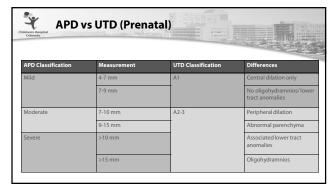


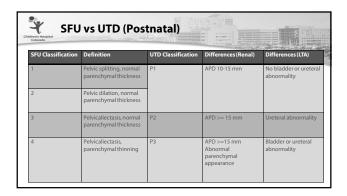


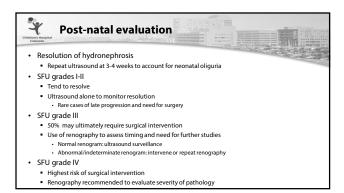


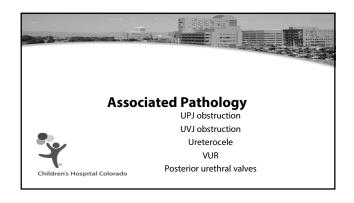


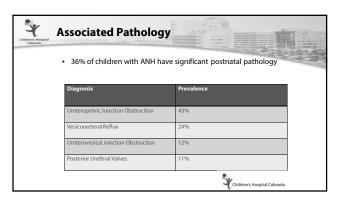


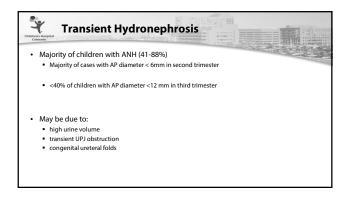


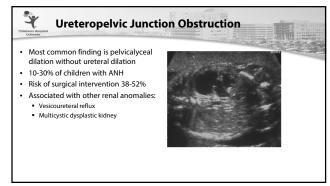


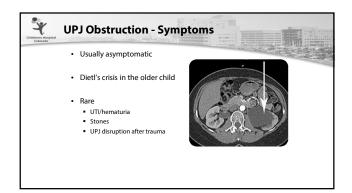


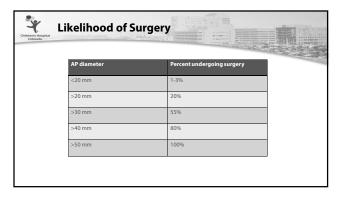


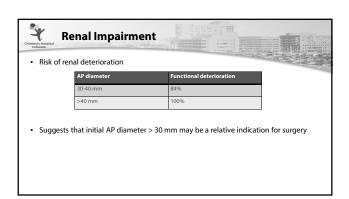


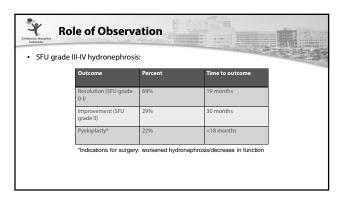


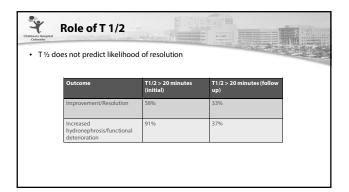


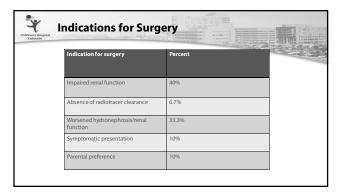


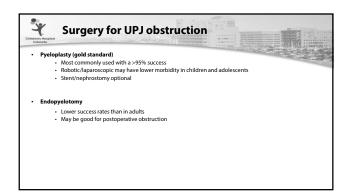


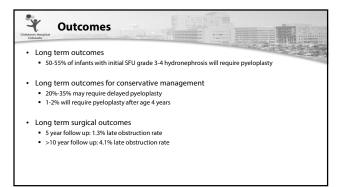


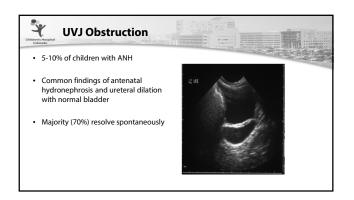


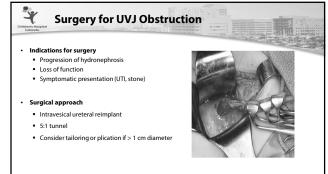


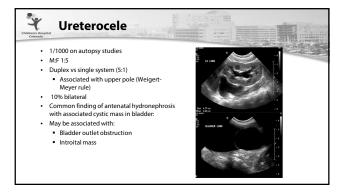


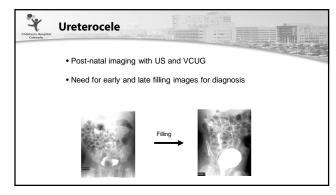


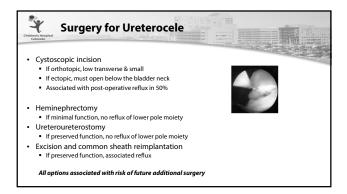


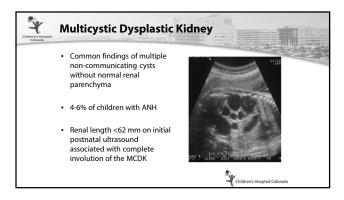


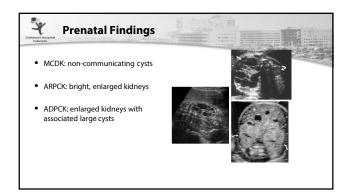


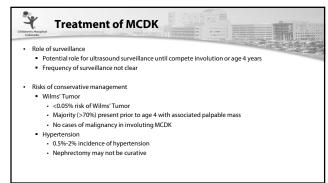


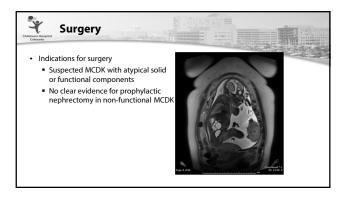


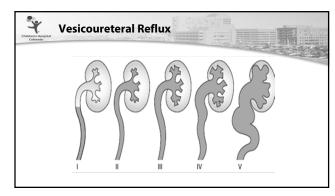


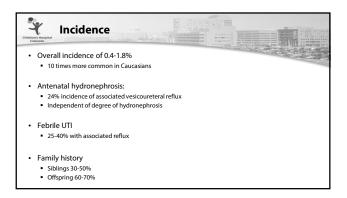


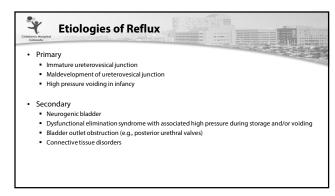


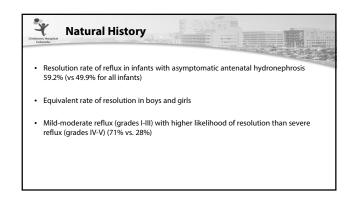


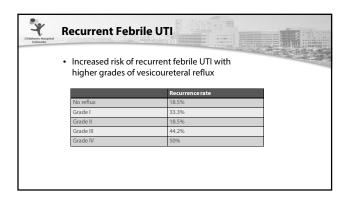


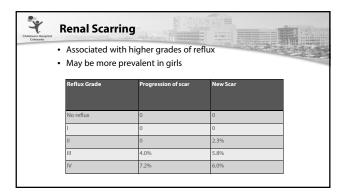


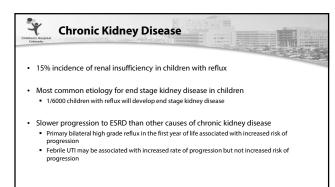


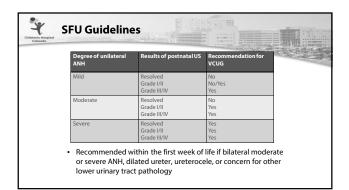


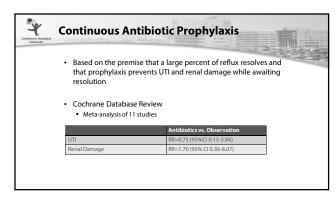


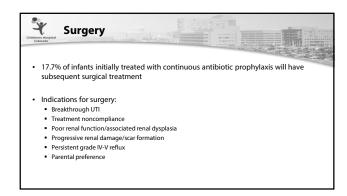


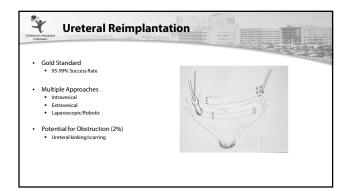


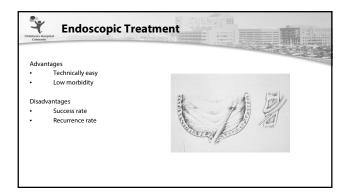


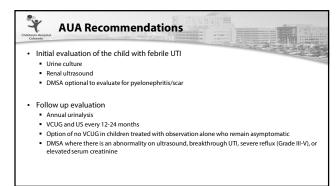


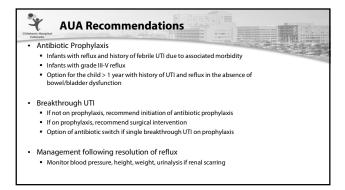


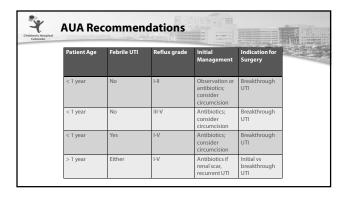


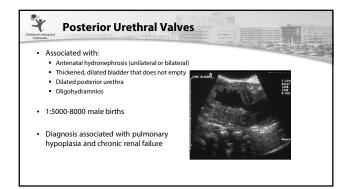


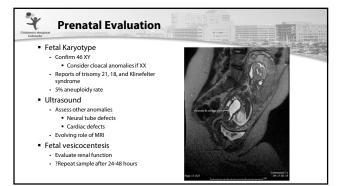


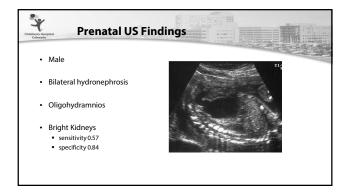


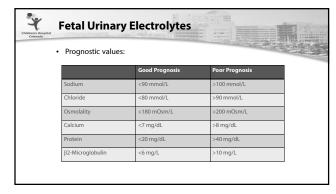


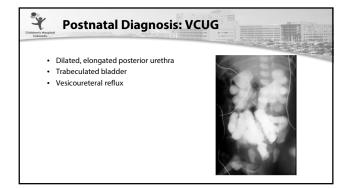


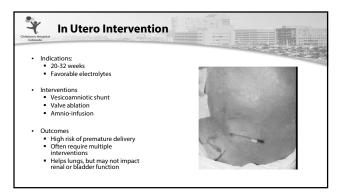


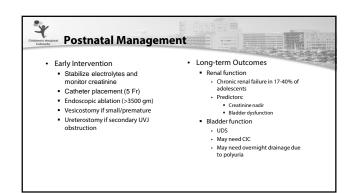


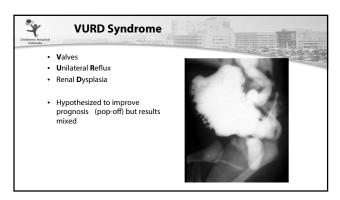


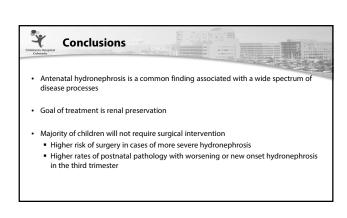


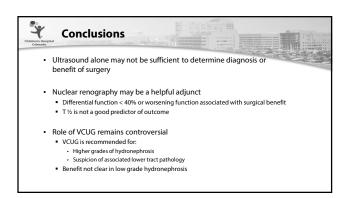


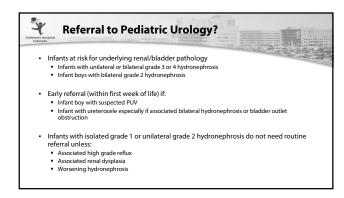








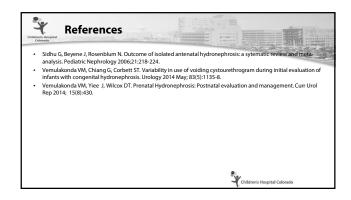












# Common Pediatric Urological Conditions-Kidneys, Genital Tract

J Todd Purves MD PhD

#### **Disclosures**

• None

#### Section 1: Genitalia

- Male
  - Foreskin: elective circumcision, phimosis, penile adhesions, balanitis, BXO
  - Meatal Stenosis
  - Hypospadias/Chordee
  - Cryptorchidism/Retractile Testes
  - Hydroceles
- Female
- Disorders of Sexual Differentiation

#### **Elective Circumcision**

"Although health benefits are not great enough to recommend routine circumcision for all male newborns, the benefits of circumcision are sufficient to justify access to this procedure for families choosing it and to warrant third-party payment for circumcision of male newborns."

-2012 American Academy of Pediatrics Circumcision Policy Statement

Pediatrics 150(3): Sept 2012

# Risks/Benefits

- Benefits
  - Lower risk of UTI (particularly in 1st year)
  - Decreased STD transmission rates including HIV
  - Lower risk of penile cancer
- Risks
  - Infection
  - Bleeding
  - Injury
  - Anesthetic risks
  - Poor cosmesis

#### Indications for Circumcision

- Recurrent balanitis/Balanitis Xerotica Obliterans
- Phimosis that restricts voiding or results in painful erections
- Obstructive uropathy
- Vesicoureteral Reflux

#### **Relative Contraindications**

- Bleeding disorders (e.g., hemophilia, Von Willebrand's, etc.)
- Medical co-morbidities that increase anesthetic risks (e.g., cardiac, pulmonary disease)

#### Methods of Circumcision

- Office techniques: Plastibel, Gomco clamps
  - Newborns (up to 3 months) with normal penile anatomy
- Surgical techniques: Tube sleeve
  - -> 3 months of age or too large for clamps
  - Penile anomalies (loose penile shaft skin, buried penis, chordee, glanular hyospadias/megameatus where urethral correction not warranted)
  - Comorbidities best managed in the OR

#### Buried Penis/Loose Shaft Skin



Hadidi H J Ped Surg 49(2): 374-9. 2012

Best managed with surgical circumcison/phalloplasty

#### **Phimosis**

- Prepuce is non-retractile during neonatal development
- Up to 10% of 3 year olds have non-retractile foreskin
- Pathological phimosis: non-retraction is due to distal cicatrix/scarring
- Problems: obstruction of urinary stream, pain with retraction, balanitis, BXO
- Non-problematic phimosis should be allowed to resolve with time and proper hygiene

# Physiological versus Pathological Phimosis





McGregor T, Pike J, and Leonard M Can Fam Physician 53(3): 445-8. 2007

#### Treatment of Phimosis

- Asymptomatic cases should be given time to resolve, using good hygiene
- 6-8 weeks of topical steroids (Betamethasone or Triamcinolone cream applied BID)
- Circumcision

#### Penile Adhesions

- Uncircumcised boys
  - Present as foreskin separates from glans
  - May result after forcefully retracting glans
- Circumcised boys
  - Penile shaft skin adheres to glans, most common with large pubic fat pad
  - May form keratinized skin bridge(s)

#### Treatment of Penile Adhesions

- Asymptomatic, non-keratinized adhesions may be treated with proper hygiene and gentle retraction
- If painful: blunt lysis if very mild, topical steroids for 6-8 weeks
- Keratinized skin bridges require sharp lysis
- If due to incomplete circumcision, revision of the circumcision may be necessary.

#### Penile Adhesions



Non-keratinized. May treat with good hygiene with gentle retraction if asymptomatic. Steroid cream or blunt lysis if symptomatic.



Keratinized skin bridges. Requires surgical excision.

Krill AJ, Palmer LS and Palmer JS Scientific World Journal

## Balanitis/BXO

- Balanitis often caused by bacteria, Candida spp., or systemic skin conditions
- Immediate treatment of balanitis: topical or oral antibiotics (erythormycin or penicillin), antifungals (clotrimazole or miconazole), steroid cream therapy (hydrocortisone)
- Balanitis xerotica obliterans: chronic inflammation, male genital variant of lichen sclerosis. Treat with circumcision

#### Balanitis/BXO

#### **Balanatis**





Huang CJ Clin Ped Emerg Med 10: 56-9. 2009



Celis S, et al J Ped Urol 10(1): 34-39. 2014

#### **Meatal Stenosis**

- Anatomically (<5Fr) in up to 20% circumcised boys
- Symptomatic in 3-8% of circumcised boys
- Trauma to exposed urethral epithelium (prevent with topical lubricant for 6 mos after circumcision)
- Narrowing of meatus
- Spraying or upward deviation of urinary stream
- Obstruction with straining.
- Dysuria
- Voiding issues/incontinence

#### **Meatal Stenosis**



Persad R. et al BIU 75: 91-3. 1995

#### Meatotomy versus Meatoplasty

- Meatotomy: simple vertical incision of ventral scarring under local anesthesia. No suturing.
  - May be done in office without general anesthesia.
  - Frequently not tolerated by children.
  - Higher re-stenosis rate (3.5%) than meatoplasty1.
- Meatoplasty: vertical incision of ventral scarring plus stitching of urothelial edge to epithelium
  - Requires general anesthesia in the OR.
  - Less psychological trauma in children
  - Lower re-stenosis rate (0.2%) than meatotomy<sup>1</sup>.

1. Godley SP et al J Pediatr Urol 11(1): 38.E1-38.E6. 2015

#### **Priapism**

- Ischemic priapism far more common in children than non-ischemic priapism
- Stuttering priapism common in children with sickle cell disease
- Most common etiologies for pediatric priapism: sickle cell disease (65%), leukemia (10%), trauma (10%), idiopathic (10%), and pharmacological (5%)

## **Neonatal Priapism**

- Extremely rare. Idiopathic but hypothesized to be due to perineal trauma during delivery
- Presence of fetal hemoglobin prevents neonatal priapism in sickle cell disease
- Zero reports of necessity for corporal injection or surgical intervention
- Observation appropriate

## **Evaluation of Pediatric Priapism**

- History must be taken and relevant blood testing (CBC, hemoglobin S) performed to uncover etiology
- Absence of pain is unreliable indicator of non-ischemic priapism.
- Color duplex ultrasonography: Frog legged position. Ischemic if high resistance, low velocity wave form with absent or low arterial flow. Close to 100% specificity and sensitivity.
- Corporal blood gas(obtained at aspiration): Ischemic priapism will show hypoxia, acidosis, hypercarbia. Glucopenia correlates with tissue damage.

#### Treatment of Pediatric Priapism

- · Management algorithms similar to adults
- Regardless of etiology, immediate relief of ischemia is paramount to prevent damage
- Anesthesia: Opiates useful for pain control of ischemic priapism and also a detumescent. Conscious sedation with local anesthesia most useful in children.
   Ketamine, in dissociative sedation, is a detumescent.
- Corporal aspiration/lavage: Lateral midshaft corporal needles placed at 3 and 9 o'clock. Prepubescent boys use 21 or 23G butterfly, Postpubescent use 19G. May need larger needle for clots. Hold pressure 5 minutes after removal to prevent hematoma.

## Treatment of Pediatric Priapism

- Intracorporal injection: AUA guidelines don't cover pediatric dosing. Monitor with telemetry, BP, HR and Pulse Ox)
  - Older than 10 yrs: Up to 10x 0.5mL aliquots of 200μg/mL phenylephrine<sup>1</sup>
  - 2-10 yrs: Irrigation up to 4x with 10mL of 1:1,000,000 epinephrine<sup>2</sup>
- As per adults, failure after ICI proceeds to shunting.

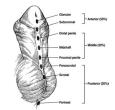
1 Donaldson, JF, Rees RW, and Steinbrecher HA J Pediatr Urol 10(1):11-24. 2014 2 Mantadikis E, et al Blood 95(1): 78-82. 2000

# Special Concerns for Sickle Cell Patients

- 30% of patients with SCD experience ED due to priapism
- Adjunct therapies (hyperhydration, supplemental oxygen, plasma alkalinization, plasmaphoresis and analgesia) should not delay corporal aspiration
- Stuttering priapism: teach 1<sup>st</sup> aid methods (exercise, urination, cold bath, ejaculation) and encourage seeking tx if longer than 2 hours, oral sympathomimetic (alpha agonists such as psuedoephedrine 0.5mg/kg QHS, PDE-5 inhibitors but not acutely, hydroxyurea 10-35mg/kg/day)

#### **Hypospadias**

- Ventrally displaced urethral meatus, ventral chordee, dorsally hooded foreskin
- 1 in 250 male births in USA
- Etiology due to genetic, endocrine and environmental factors but largely unknown



#### Kraft KH, Shukla AR and Canning DA Urol Clin North Am 37(2): 167-81. 2010

#### **Evaluation of Hypospadias**

- Typically diagnosed at child's first exam.
- When diagnosed during circumcision, complete the procedure.
- Assess location and patency of meatus, severity of chordee, size of penis
- Severe hypospadias or hypospadias and cryptorchidism warrant karyotype and DSD workup

# Associate findings

- Hernia/Cryptorchidism-DSD workup
- DSD-27% in boys with hypospadias and UDT
- Enlarged prostatic utricle- more common in severed hypospadias. Consider when boys present with epididymitis, urethral stone or are difficult to catheterize.

#### **Goals of Treatment**

- Glanular meatus to allow voiding in standing position. Properly positioned ejaculate for fertility.
- Straight penis to allow sexual function.
- Cosmesis with conical glans and supple penile shaft skin

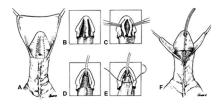
#### Androgen Stimulation

- Boys with stretched penile length below 3<sup>rd</sup> percentile or too small for reconstruction may require androgen stimulation
- · No standard of treatment
- Common strategy is for 25mg testosterone enanthate IM injection 6 and 2 weeks prior to surgery
- Some advocate earlier administration to decrease bleeding

#### Types of Hypospadias Repair

- Distal: Meatal advancement and glanuloplasty
- Distal and Proximal: Tubularized incised plate urethroplasty
- Proximal: Island onlay hypospadias repair (useful for narrow urethral plate), Transverse island tube repair (useful with more severe chordee), Two stage repair (1st: scrotoplasty, chordee repair often with transection plate, Byar's flaps. Approximately 6 months later, 2nd: tubularize urethra to glans, complete repair)

#### **Tubularized Incised Plate Urethroplasty**



Snodgrass TW Urology 54(1): 6-11

# Tips for the TIP

- Width of urethral plate, after incision, must accommodate 6 Fr catheter
- Midline incision of plate down to corporal bodies
- Do not extend distal to plate to avoid meatal stenosis
- Tubularize urethra with 2 layer subcuticular closure using 6-0 polyglactin over 6-8 Fr stent
- Cover urethroplasty with dartos flap. Tunica vaginalis flap if dartos not available.
- Compression dressing and keep stent approximately one week

#### Complications of Hypospadias Repair

- Overall complication rate for midshaft to distal hypospadias about 10%
- Fistula: observation for 6 months for healing and possible spontaneous resolution. Then simple or complex repair.
- Strictures: Dilation and DVIU possible for very mild cases. Frequently, excision of repair and buccal grafting with subsequent repair needed.
- Meatal stenosis/diverticuli: cystoscopy to assess obstruction
- Recent literature suggests higher rates of complications than previously reported.

# Cryptorchidism/Retractile Testes

 Evaluation and management of undescended testes should follow the 2014 AUA guidelines<sup>1</sup>



1 Kolon TF et al J Urol 192(2): 337-45. 2014

## **Evaluation of Cryptorchidism**

- Testicles descend into scrotum during 3<sup>rd</sup> trimester
- 3% of boys born with UDT, 1% at one year
- Testosterone surge at 1 to 3 months of age
- Undescended testes should be treated at 6 months corrected for gestational age
- UDT and hypospadias or bilateral UDT prompt workup for disorders of sexual differentiation
- · Imaging not useful

#### Retractile Testes

- · Testes have descended
- Strong cremasteric reflex: cold, fear, touch
- Ask parents/caregivers if they see testes in scrotum during bathing/diaper changes
- Reflex diminishes at puberty-No Surgery!
- Some small risk of ascent- annual examination

#### **Cryptorchidism Treatment**

- No role for hormonal therapy
- Exam under anesthesia to identify position and plan surgical approach
- Palpable testes undergo open inguinal or scrotal (Bianchi) approach
- Non-palpable testes on EUA require diagnostic laparoscopy/abdominal exploration
- Primary orchidopexy most successful (96%) but not always possible. 1 (79%) or 2 (86%)stage Fowler Stephens for short vessels.
- Testicular vessels must be identified for diagnosis of vanishing testis

#### Long Term Consequences of UDT

- Higher risk of testis cancer. Earlier reports may have overestimated risk.
- Orchidopexy prior to puberty decreases risk
- Paternity rates for a) no UDT 94%, b) unilateral UDT 90% and c) bilateral UDT 62%
- Orchidopexy prior to 18 months of age may help preserve fertility
- Testis biopsy may have use in predicting fertility but is limited in clinical use
- Cosmesis

# Hydroceles

- Overwhelming majority of pre-pubertal hydroceles are communicating
- Communicating hydroceles result from migration of peritoneum during testis descent
- No abdominal wall defect, treat with high ligation
- In term infants, surgery delayed 18-24 months to allow spontaneous closure of tunica vaginalis
- Premature infants at higher risk of developing strangulated hernia and so repaired urgently

#### Vaginal Masses

- Paraurethral cysts or Skene's cysts
- Prolapsed ureterocele
- Urethral prolapse
- Rhabdomyosarcoma

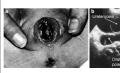
# Paraurethral cysts (Skene's cysts)

- Presents in infancy as smooth whitish paraurethral mass
- Most rupture/resolve in a few months without intervention
- If symptomatic with urinary spraying or persistent, simple excision or needle aspiration



Fujimoto T et al J Ped Surg 42(2): 400-3. 2007

# Prolapsed ureterocele





- Large purplish mass in vestibule, eccentric
- Associated with upper pole of dilated system
- Can cause urinary obstruction, UTI
- Renal/bladder ultrasound to aid diagnosis

# **Urethral Prolapse**





Nguyen K and Jacobs K Consultant 15(3):138-9 2016

- Circumferential protrusion of urethra
- Presents with bloody spotting; dysuria/pain
- African American girls 4-5 years
- 1) Sitz baths, treat constipation 2) conjugated estrogen cream 3) surgical excision

#### Vaginal Rhabdomyosarcoma



https://web.duke.edu/pathology/bones/bones

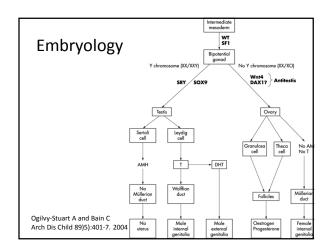
#### Labial adhesions

- Common 3 months-3 years
- Asymptomatic, voiding problems (dribbling), UTI
- Asymptomatic should be observed. Up to 80% resolve in one year
- Girls in diapers have high recurrence after treatment
- Conjugated estrogens or estradiol cream (Estrace) bid for 2-6 weeks
- Gentle blunt lysis with Q tip and lubricant. In OR or office with EMLA anesthesia

Syed-Ansari T, et al Glob libr women's med (ISSN:1756-2228) 2008; DOI 10.3843/GLOWM.10010

# **Disorders of Sexual Development**

- Embryology
- Nomenclature
- Gender Assignment
- Surgical Management
- Gonadal Tumors
- Hormone Replacement
- Psychosocial Issues



#### Disorders of Sexual Differentiation

• 2006 Revision of Nomenclature

Previous	Current
Intersex	DSD
Male pseudohermaphrodite, undervirilization of an XY male, and undermasculinization of an XY male	46,XY DSD
Female pseudohermaphrodite, overvirilization of an XX female, and masculinization of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

Lee PA et al Pediatrics 118(2): E488-500. 2006

Sex Chromosome DSD	46,XY DSD	46,XX DSD
45,X (Turner syndrome and variants)	Disorders of gonadal (testicular) development: (1) complete gonadal dysgenesis (Swyer syndrome); (2) partial gonadal dysgenesis; (3) gonadal regression; and (4) ovotesticular DSD	Disorders of gonadal (ovarian) development: (1) ovotesticular DSD; (2) testicular DSD (eg, SRY+, duplicate SOX9); and (3) gonadal dysgenesis
47,XXY (Klinefelter syndrome and variants)	Disorders in androgen synthesis or action: (1) androgen biosynthesis defect (eg. 17-hydroxysteroid dehydrogenase deficiency, SaRD2 deficiency, StaRD2 deficiency, StaRD2 tedriciency, StaR	Androgen excess: (1) fetal (eg, 21- hydroxylase deficiency, 11- hydroxylase deficiency); (2) fetoplacental (aromatase deficiency, POR [P450 oxidoreductase)]; and (3) maternal (luteoma, exogenous, etc)
45,X/46,XY (MGD, ovotesticular DSD)		Other (eg, cloacal exstrophy, vaginal atresia, MURCS [Müllerian, renal, cervicothoracic somite abnormalities], other syndromes)

# Indications for DSD Evaluation (Newborn)

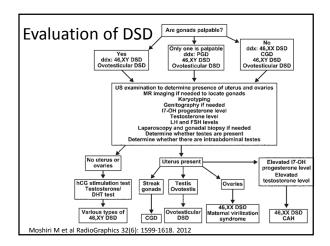
- Ambiguous genitalia
- Apparent female with clitoromegaly, posterior labial fusion, inguinal/labial mass
- Apparent male with bilateral UDT, micropenis, perineal hypospadias, any hypospadias with UDT
- · Family history
- Discordance between phenotype and karyotype

# Indications for DSD Evaluation (older children and young adults)

- Delayed/incomplete puberty
- Failure to initiate menarche
- Virilization of female
- Inguinal hernia in females
- Gynecomastia in males
- Cyclic gross hematuria in males
- Newly recognized genital ambiguity

# Ambiguous Genitalia

- Emergent condition in newborn
- Most common diagnosis is congenital adrenal hyperplasia due to 21 hydroxylase deficiency
- Failure to recognize and treat electrolyte imbalances can be fatal



#### Gender Assignment

- · Very controversial
- Do not rush! Avoid definitive statements prior to full evaluation.
- Factors include: Etiology/diagnosis, appearance and function of genitalia, surgical options, hormone replacement requirements, fertility, family/culture
- Current understanding and practice often leads to incorrect outcomes

#### Hormone Replacement

- Hypogonadism: gonadal dysgenesis, errors in sexsteroid biosynthesis, androgen insensitivity
- Hormonal replacement to initiate puberty: induce secondary sexual characteristics, overall growth, optimal bone development
- Males: intramuscular depot testosterone, oral testosterone undecanoate, transdermal
- Females: estrogen supplements, progestin started after 1-2 years of continuous estrogen OR development of breakthrough bleeding
- Pediatric endocrinology

# Surgical Management

- Trend towards delaying surgery until consent from patient is possible
- · Early "normalization" versus uncertainty
- Functional concerns may prohibit delay
  - Cloacal anomalies repaired to prevent infection, urinary obstruction, allow continence
  - Vaginoplasty to allow egress of menses
  - Symptomatic Mullerian remnants
  - Retained testicular tissue will cause virilization in children raised as females
  - Retention of testicular tissue can negatively impact fertility in cases of bilateral ovatestes
- Penile reconstruction pre vs post puberty
- Concerns about malignancy

#### **Gonadal Tumors**

- Testicular cancer risk highest in patients with Y chromosomal material, abdominal gonads, gonadal dysgenesis/streak gonads
- Dysgenetic gonads/streak gonads risk pre-pubertal malignancy-removed early
- PAIS with abdominal testes may have cancer risk as high as 50%
- CAIS very low risk of pre-pubertal malignancy and may benefit from hormonal production from native testes
- 46 XX DSD patients without Y chromosomal materialno increased risk

# **Psychosocial Issues**

- DSD patients experience high rates of depression, anxiety, suicidal ideation, suicide attempts
- Gender identity
- Gender role
- Sexual Orientation
- Critical to enlist psychologists/psychiatrists with relevant expertise
- Address needs of both patients AND parents
- Trends towards earlier disclosure

#### Section II: Kidneys

- Embryology
- Renal agenesis/Duplication
- Ectopic kidney
- Ureteropelvic Junction Obstruction
- Cystic kidney disease
- Nephrolithiasis

## **Upper Tract Embryology**



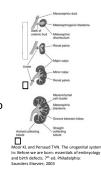
- Pronephrosis involutes by 4th week
- Mesonephrosis: principal excretory organ 4-8 weeks, then degenerates
- Metanephros: Originates from intermediate mesoderm and mesonephric duct as ureteric bud.

#### Development of the ureter

- Pronephric duct forms from anterior pronephric tubules and then serves as mesonephric duct, giving rise to ureter.
- Independent caudal growth of nephric duct to the cloaca.
- Ureter is outgrowth of nephric duct while renal tubules arise from adjacent metanephric blastema

# **Development of Kidney**

- Cephalad growth of ureteric bud, contacts mesoderm of nephrogenic cord
- Metanephric cap enlarges and undergoes differentiation to form nephrons
- Ureteral bud expands to form renal pelvis and outpouchings to form primary collecting ducts
- Rotation so renal pelvis faces aneriorly



# Renal Agenesis

- Usually results from failure of ureteric bud to develop. Less likely involution of dysplastic kidney.
- Ipsilateral ureter and hemitrigone also absent.
- Defect may also affect other mesonephric duct derivatives: seminal vesicles, vas deferens ( can be bilateral), and epididymis.
- Prognosis of unilateral agenesis excellent though some suggestion of increased renal dysfunction, proteinuria and HTN
- Bilateral renal agenesis incompatible with life.
   Only anecdotal survival beyond newborn period

# Anomalies Associated with Unilateral Renal Agenesis

- 30-70% overall
- Vesicoureteral reflux: 28-41%
- Ureterovesical obstruction: 11-18%
- Ureteropelvic junction obstruction: 6-7%
- Can also affect heart, GI tract, genital and skeletal systems
- Higher incidence of single umbilical artery

#### **Renal Duplication**

- Overexpression of glial cell –derived neurotrophic factor (GDNF)-RET induces multiple ureteral bud formation
- If ureteric bud bifurcates prior to effacing metanephrosis-incomplete duplication with common distal ureter results
- Creation of two ureteric buds results in complete duplication

#### Consequences of Duplicated Kidney

- Often an inconsequential variant of normal
- Weigert-Meyer rule
  - Lower pole: ureter inserts cephalad to upper pole.
     VUR is common. Obstruction less common, usually
     UPJ and less likely at UVJ
  - Upper pole: ureter inserts caudal to lower pole. Can be ectopic and insert into (boys) bladder, prostatic urethra or Wolffian structures such as seminal vesicles, ejaculatory ducts, epididymis or vas deferens while in girls into the bladder, urethra or vagina
- Ectopic ureter always above external sphincter in boys but either above/below in girls
- Ureteroceles common at upper pole insertion

## **Ectopic Kidney**

- Simple ectopy: failure to ascend normally.
- · Crossed ectopy: with or without fusion
- Renal fusion: fusion of the metanephroi prior to ascent results in horseshoe or crossed fused ectopia. Ureteral orifices are orthotopic.
- Ectopic kidney may be clinically inconsequential.
   Higher risk of obstruction due to aberrant vessels,
   kinking due to malrotation. Hydronephrosis, stone
   and infection more common.

#### Horseshoe Kidney







ghavi K, Kirkpatrick J an Iirjalili SA J Ped Urol 12: 75-80. 2016

- Unable to ascend. "Held back by inferior mesenteric artery", though immediately inferior in 40%
- Obstruction common due to malrotation, ureter coursing over parenchyma, highly variable vascular structure
- Division of isthmus rarely needed for de-obstruction

## **Ureteropelvic Junction Obstruction**

- · Intrinsic Obstruction (narrow lumen)
  - Aperistaltic segment arises from premature arrest of ureteral differentiation near UPJ
  - Persistence of fetal folds in the ureter
  - Extreme lack of smooth muscle differentiation in a region that normally has less smooth muscle
- Extrinsic Obstruction
  - Crossing vessels
- Adhesions/fibrosis from infection or instrumentation
- Secondary Obstruction
  - Compensatory hydonephrosis can exacerbate original cause
  - Association with high grade reflux but not common enough to establish causality

# Diagnosis of UPJ obstruction

- Historically found after infection, pain, stones or hematuria
- Currently, most are diagnosed on prenatal US
- Management less certain in asymptomatic cases (the majority)

#### Evaluation of UPJ obstruction

- Diagnosis is made as part of evaluation for prenatally diagnosed hydronephrosis
- Main question "Is there significant enough obstruction to cause pathological changes?"
- Clinical signs of pain, stone formation, bleeding and infection all favor repair

#### **Defining Obstruction**

- Typically motivated by clinical signs, worsening hydronephrosis on serial US, or initial severe presentation (gr3-4)
- Nuclear renal scan
- Resistive index on Doppler US
- · Whitaker test

#### Ultrasound

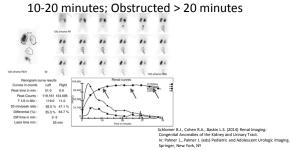
- Resistive index= (peak systolic velocity-end diastolic velocity)/peak systolic velocity
- RI > 0.70 suggests obstruction
- Initial studies encouraging but not supported in later investigations
- Common for babies (<1 yr) to have RI >0.70 (up to age 4)
- Not frequently used if other modalities available

# **Nuclear Renal Scan**

- Most common study using <sup>99m</sup>TC-MAG3 with Lasix diuretic challenge
- Child must be at least 2-3 months of age
- Bladder catheter for VUR, children who cannot volitionally void, bladder pathology or pelvic kidney
- Standardize timing of Lasix. F+15 mins
- RRF< 40% relative indication for surgery.</li>
   Obstruction can delay uptake-appears worse
- Elicitation of Dietl's crisis should be evaluated

#### MAG3 with Lasix Renal Scan

 Unobstructed T1/2 < 10 minutes; Equivocal 10-20 minutes; Obstructed > 20 minutes

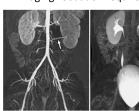


#### Whitaker Test

- Useful when massive dilation or poor renal function confounds nuclear scan
- Percutaneous administration of contrast at 10mL/min while monitoring of infusion and intravesical pressure
- Normal 0-15cm H2O, Equivocal 15-22cm H2O, Obstructed >22 cm H2O

#### Other modalities

- · CT: rarely used, very high radiation
- MR Urogram: Emerging technology without ionizing radiation. Can combine functional with anatomic imaging. Sedation requirement in younger patients



Parikh KR et al. Ped Radiol

# Surgical Repair of UPJ obstruction

- Timing controversial. Earlier repair affords greater recovery potential.
- Dismembered pyeloplasty versus Y-V plasty.
   Latter may be useful for high insertions.
- Open versus laparoscopic
- Endoscopic approach
- Stenting or not

#### Open versus Laparoscopy

- Significant pain/recovery advantage for laparoscopy in older children
- Dorsal lumbotomy or small subcostal incision with infants and younger children.
- Lap retroperitoneal approach less risky but technically more challenging

## Endopyelotomy

- Retrograde or antegrade with ballon, Accusize, or laser.
- Significantly lower success rate compared to open/lap repair of primary UPJO (ca. 60 vs 90% success rate)
- Possible bleeding with crossing vessel
- Stenting for 6 weeks post op
- May be useful after failed primary repair but most of those patients undergo repeat repair

#### **Post-op Stenting**

- 4-6 weeks
- Double j stents common but require second anesthesia in children. Induces VUR-many leave Foley 1-2 days post op.
- Ureteropyelostomy tube can be brought out of abdominal wall. Removed without anesthesia.
- Non-stenting. Greater risk of leakage and acute obstruction from inflammation/edema or clots.

#### Pediatric Renal Cystic Disease

- Genetic: autosomal recessive polycystic disease, autosomal dominant polycystic kidney disease, glomerulocystic kidney disease, medullary cystic dysplasia
- Non-genetic: renal dysplasia, multicystic dysplastic kidney, obstructive cystic dysplasia, nongenetic nondysplastic cysts, simple cyst, multilocular cyst, medullary sponge kidney

#### **Evaluation of Pediatric Renal Cysts**

- · Family history
- Physical exam: associated anomalies, palpable kidneys/cysts
- Ultrasonography
  - Size, number, complexity and location of cysts
  - Echogenicity of parenchyma compared to liver or spleen
  - Corticomedullary differentiation

# Autosomal recessive polycystic kidney disease

- Often fatal in infancy due to renal failure and hepatic fibrosis
- Cystic dilation of tubules in the medulla, hepatic fibrosis
- Large hyperechoic kidneys, no corticomedullary differentiation

Avni FE et al Ped Radiol 35(5): 405-14. 2006



# Autosomal Dominant Polycystic Kidney Disease

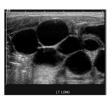
- Positive family history about 50%
- Cysts may not develop until adulthood
- US often shows moderately enlarged kidneys with hyperechoic cortex, hypoechoic medulla
- Cysts only treated (excision, marsupialization) if symptomatic-pain, infection, bleeding, obstruction





Avni FE at al Ped Radiol 35(5):

#### Imaging of MCDK



Raviv-Zilka L et al Urol Sci 27(3): 158-60. 2016



Nepple KG and Cooper CS in Pediatric Urology for the Primary Care Physician, Rabinowitz et al (eds.)Current Clinical Urology. Springer. New York.2014

# Multicystic Dysplastic Kidney

- Thought to result from complete obstruction early in development or aberrant epithelial/mesenchymal signaling
- Ultrasound shows multiple non-connecting cysts of variable size, variable amount of echogenic stroma, no normal cortex or medulla, irregular contour, no collecting system
- Nuclear scan shows no activity- useful if needed to rule out severe obstructive hydronephrosis or cystic Wilm's tumor

#### **Associated Anomalies**

- Overall 5-48%
  - Contralateral VUR
  - Contralateral UPJ obstruction
  - Contralateral UVJ obstruction
  - Less likely- ureterocele, horseshoe kidney

#### Natural course

- Over half involute by age 10
- Compensatory hypertrophy found in over 90% by adolescence
- Hypertension develops at similar rates to general population. Nephrectomy cures about half.
- Malignancy extremely rare with proper imaging

## Management of MCDK

- Confirmatory nuclear scan only needed if ultrasound ambiguous
- VCUG if infections present or if contralateral kidney is abnormal/hydronephrotic
- Serial US imaging controversial. Common to follow initial postnatal US at one year to evaluate contralateral kidney
- Nephrectomy rare. Indications would be for intractable HTN, enlargement, infection

#### Simple Renal Cysts

- Most are asymptomatic, incidental findings with no clinical relevance
- No advanced imaging unless unclear



Avni FE et al Ped Radiol 35(5): 405-14. 2006

# Management of Simple Cysts

- Annual US to assess for enlargement
- Indications for Surgery
  - Pain due to enlargement (usually >10cm)
  - Infection
  - Obstruction
- Surgical Strategies
  - Open/laparoscopic excision
  - Open/laparoscopic marsupialization
  - Aspiration and sclerosis- high rates of recurrence

# Pediatric Nephrolithiasis

- Not as common in children but incidence rising over past decades. Environmental and dietary causes suspected.
- More common in children with metabolic, genetic or anatomic abnormalities

#### **Evaluation of New Stone Patients**

- · History and Physical
- Diet: Low fluid intake, high sodium, excessive protein, ketogenic diets, all increase risk
- Medications: vit D, Ca, Vit C, diuretics, steroids, uricosuric drugs and antibiotics (indinavir, ceftriaxone)
- Family history: may be due to genetics or shared environment/diet

#### Co-morbid Conditions

- Urinary tract obstruction
- Vesicoureteral reflux
- Immobilization
- · Neurogenic bladder
- · Inflammatory bowel disease
- Short gut syndrome
- Cystic fibrosis
- · Seizure disorders

# Metabolic Abnormalities (Initial evaluation)

- List is extensive. Unless provider specifically trained, referral to pediatric nephrology.
- Most common include hypercalciuria, hypocitraturia, hyperoxaluria, hyperuricosuria, cystinuria
- Two 24 hour urine collections recommended due to variability. Need to adjust expected range based on age/size.
- Comprehensive metabolic panel. Must collect at same time of urine collection.

#### **Pediatric Stone Imaging**

- CT scan gold standard for adults, very high radiation.
- Ultrasound first and often only imaging study needed for children.
- Reserve CT where there is clinical suspicion and a negative US AND the result will change management.
- Abdominal X ray helpful after US to determine potential for ESWL

#### Acute Management

- Analgesia: Acetaminophen, NSAIDs (Toradol), narcotics
- · Indications for intervention
  - Infection
  - Impassable stone (>5mm)
  - Intractable pain
  - Failed trial of passage and patient desire
- Ureteral stenting versus Nephrostomy tube

# **Treatment of Stones**

- Medical expulsive therapy: Controversial as in adults. Tamsulosin 0.4mg qd with 4-6 week trial.
- Ureteroscopy: Stenting 4-6 weeks prior may be necessary for access, decrease trauma.
- Percutaneous nephrolithotomy: Avoids ureteral trauma, new "mini-perc" equipment
- Extracorporal shock wave lithotripsy: Effective in children, does require passage of fragments

# Prevention of Pediatric Stones Metabolic Abnormality Conservative Management Hypercalciuria Increase fluid intake Limit dietary sodium intake Limit detary sodium intake Limit dietary sodium intake Avoid excessive protein intake Normalize vitamin D status Hypocitraturia Encourage intake of dietary calcium Increase fluid intake Reduce dietary oxalate Consume RDA of dietary calcium Treat fat malabsorption, if present Probiotics Hyperuricosuria Increase fluid intake Decrease fluid intake Decreas

# Fluid Recommendations

- Increase the Dilution, Decrease the Pollution
- Fluid intake should be minimum of 1.5-2L/m²/day which translates to:

	AGE	Minimum (mL)/day
	Infant	750
	<5 years	1000
	5-10 years	1500
	>10 years	2000

**END OF CHAPTER** 

# Common Pediatric Urology Conditions:

Congenital Disorders, Bladder

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Oakland | San Francisco

## Congenital Disorders of the Bladder

■ I have no disclosures

# Congenital Disorders of the Bladder

- Neurogenic bladder
- Lower urinary tract obstruction
- Prune Belly Syndrome
- Exstrophy-epispadias complex
- Urachal abnormalities
- Bladder diverticulum
- Bladder masses

# Congenital Disorders of the Bladder

- Neurogenic bladder
  - Spina bifida: 29.01/100,000
- Lower urinary tract obstruction
  - Posterior urethral valves: 11.02/100,000
- Prune Belly Syndrome
  - **3.28/100,000**
- Exstrophy-epispadias complex
  - Bladder exstrophy: 1.63/100,000

Lloyd 2013

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Lloyd 2013

# Neurogenic Bladder

- Spina bifida
- Tethered cord
- Sacral agenesis
- Cloacal anomaly
- Anorectal malformation
- Cerebral palsy

# Neurogenic Bladder

- Spina bifida most common cause
  - Birth prevalence: 29.01/100,000 children
- Myelomeningocele accounts for >90% of all open spinal dysraphic states

# Spina Bifida

- Majority of defects occur at lumbar vertebrae
- Level of vertebral defect does not correlate with neurologic lesion
- Neurologic sequelae depend on which neural elements evert into the meningocele sac
- Neurologic lesion is a dynamic condition that can change with linear growth

# Neurogenic Bladder

- Normal lower urinary tract function
  - Low pressure urine storage
  - Periodic voluntary emptying
- Neurogenic bladder
  - Bladder dysfunction caused by neurologic malformation or damage

# Neurogenic Bladder

- GU complications major source of morbidity
  - Incontinence, recurrent UTI, chronic renal insufficiency, and end-stage renal disease
- Optimal urologic care not known
  - Routh 2016: CDC-sponsored, prospective protocol for management of children with spina bifida
    - 5-yr outcomes assessment: UTIs, renal function, renal scarring and clinical process improvements

# Neurogenic Bladder Goals

- Preservation of low pressure storage and efficient emptying
- Prevention of upper tract changes and maintenance of normal renal function

#### **Evaluation: Ultrasound**

- A window into bladder behavior to detect lower tract changes prior to upper tract damage
- Not good for detection of renal scarring
  - Veenboer 2015: 10% with scars on ultrasound, 46% with scars on DMSA scan

## **Evaluation: Urodynamics**

- Assess intravesical pressures, capacity and detrusor leak point pressure (DLPP)/end fill pressure (EFP)
- Recommended urodynamics schedule variable
  - CDC protocol
  - Newborn period

  - Yearly during 1st 3 years of life
     Repeat each year if VUR present on last UDS until age 5
- Urodynamics if clinical change: new hydronephrosis, new incontinence, UTI

## Evaluation: Kidney Function

- Serum creatinine between 1-3 months of age and then yearly thereafter
  - Cordeiro 2008: Serum creatinine unreliable in spina bifida patients from decreased muscle mass (muscle wasting) and short stature (scoliosis)
- Renal scan at 1-3 months of age for baseline split renal function

# Management: Clean intermittent catheterization (CIC)

- Before CIC: renal failure most common cause of death at all ages in spina bifida patients
  - Sawin 2015: 74% of patients in National Spina Bifida Registry use CIC
- Indications for, timing of, and schedule of CIC varies in newborn period
  - Joseph 1989: Easier acceptance of CIC by parents and children as they grow older if initiated earlier

# **Management: Medications**

- Anticholinergic medications should be initiated in hostile bladders
  - DLPP/EFP > 40cm H<sub>2</sub>0
  - Neurogenic detrussor overactivity
  - Detrusor sphincter dyssynergia
- 0.2 mg/kg oxybutynin orally tid

# **Management: Medications**

- Prophylactic antibiotics
  - Antibiotic use in vesicoureteral reflux related to neurogenic bladder is controversial
  - CDC protocol: used if grade V reflux or lower grade reflux + hostile bladder

# **Surgical Management:** Intradetrusor Onabotulinumtoxin A

Intradetrusor Onabotulinaumtoxin A = Botox

- Dosing: 10-12 units/kg, max dose 300 units
- Used for a variety of conditions
  - Cumulative dose: ≤360 units in a 3 month interval
- Adverse effect from risk of toxin spread
  - Asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysarthria, breathing difficulty, paralysis of respiratory muscles and intubation

# Surgical Management: Botox

- Khan 2016
  - 50%: no improvement in incontinence
  - If response, mean duration: 4.6 months
- Kask 2014, Tiryaki 2015
  - Poorest response if severely impaired compliance or fibrotic bladder
  - Significant increase in capacity and compliance when main indication is detrusor overactivity

# Surgical Management: Botox

- Disadvantages of Botox
  - Requires regular injections with recurrent anesthesia exposure
  - Chohan 2015: loss of efficacy over time

# Surgical management: Surgical Reconstruction

- If fail medical and intravesical treatment options, surgical reconstruction performed
  - Bladder failure with intact sphincter and ability to catheterize per urethra: bladder augmentation
  - Bladder augmentation with non intact sphincter: bladder augmentation with outlet procedure and continent catheterizable channel

## Congenital Disorders of the Bladder

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Lloyd 2013

# Lower Urinary Tract Obstruction

- Intrinsic
  - Posterior urethral valves
  - Urethral atresia
  - Anterior urethral valves
  - Congenital megalourethra
- Extrinsic
  - Outlet compression from pelvic mass

#### **Posterior Urethral Valves**

- Obstructing membrane in posterior urethra
- Most common cause of lower urinary tract obstruction in males
- Birth prevalence: 11.02/100,000
- Accounts for 17% of renal failure in kids

# Posterior Urethral Valves

- Obstruction develops early in gestation
  - Urethra develops at 14 weeks of gestation
  - Valves present prior to this time
  - Obstruction begins with urine production
- Bladder and upper urinary tract are exposed to elevated pressure during development
  - Affects bladder development and function
  - Causes renal injury

#### **Posterior Urethral Valves**

- Usually detected prenatally
  - Hydronephrosis
  - Distended, thick-walled bladder
  - Oligohydramnios
  - "Keyhole" sign

#### Presentation

- Cases not detected prenatally
  - If present after birth may see poor urinary stream, UTI, and/or failure to thrive
  - Older children may present secondary to diurnal enuresis, UTI, severe LUTS (dribbling, retention, hematuria)

# **Fetal Ultrasound Findings**





# Keyhole appearance





# Keyhole appearance





# Postnatal Management

- Bedside management
  - Catheter placement
  - Labs: monitor electrolytes and renal function
  - Antibiotics
- Imaging
  - RBUS
  - VCUG

#### **VCUG**



# **Surgical Intervention**

- Circumcision + ...
  - Bader 2013: 83% reduction in UTI
- Valve ablation
- Cutaneous vesicostomy
  - Indications for vesicostomy
    - <2000g infant</p>
    - Urethra can't accommodate cystoscope

#### Vesicoureteral Reflux

- 50% will have VUR at diagnosis
- After ablation VUR resolves in up to 1/3
  - May take months to several years
  - More likely to resolve if bilateral
  - Less likely to resolve if kidney function is poor

Smith 1996, Hassan 2003

#### Vesicoureteral Reflux

- Persistent high-grade VUR usually from persistent bladder dysfunction
  - High bladder storage pressures and poor drainage
- High risk for complications due thick-walled bladder and voiding dysfunction
  - UDS, check for persistent valve remnants
  - Rarely reimplant: only if persistent infection <u>AND</u> bladder function adequately managed

Kim 1997

# Hydronephrosis

- Most have severe hydronephrosis at diagnosis
  - Not always associated with VUR
  - Urine concentrating defect and polyuria
- ~50% of nonrefluxing hydronephrois resolves with valve ablation
- Persistent hydronephrosis common

Tietjen 1997 Glassberg 1982

# Valve Bladder Syndrome

#### Mitchell 1982

 Despite valve ablation intrinsic bladder dysfunction leads to deterioration of the upper tracts and incontinence

# Pathophysiology

- Compensated phase
  - Bladder wall hypertrophy develops
  - Bladder generates high voiding pressure
  - Bladder usually able to empty

## Pathophysiology

- Decompensated phase
  - Further hypertrophy
  - Detrusor begins to decompensate
  - Postvoid residual increases
  - Storage pressure rises

# Pathophysiology

- Elevated intravesical storage pressures transmit to upper tracts
- Elevated renal pelvic pressures overtime can affect renal morphology and function
  - Decreased renal concentrating ability
  - Decrease in GFR
- Overtime polyuria and compensatory polydipsia

# Valve Bladder Variability

- Hyperreflexic (uninhibited contractions)
  - May respond to anticholinergic therapy
- Small noncompliant
  - May respond to anticholinergic therapy
  - May need CIC
  - May need augmentation
- Myogenic failure
  - Need CIC

# Breaking the cycle...

- Start with timed voiding, double voiding
- Monitor closely
- Management guided by ultrasound and urodynamics
- Koff 2002
  - This is not a permanent state...It is an induced condition from polyuria, impaired bladder sensation, and PVR

# Breaking the cycle...

- CIC plus overnight catheter drainage
  - Reduces the strain of high output on urinary tract
  - Provides prolonged period of rest
  - Results: improved GFR, improved bladder compliance and capacity, decreased hydronephrosis

Koff 2002, Holmdahl 2003

#### Incontinence

- Up to 80% with delayed day and night continence at 5 years, 50% at 12 years, improves by 20's
- Causes: poor bladder sensation, poor compliance, detrusor instability, and polyuria
- Treatment varies: timed/double voiding, anticholinergics, CIC...augmentation

Churchill 1990, Smith 1996

## **Prognosis**

- Predictors of poor renal function
  - Ultrasound
  - dysplasia estimation, severe hydronephrosis
  - Creatinine at 1 year (1 ng/dL)
  - VUR
    - Bilateral VUR
  - Recurrent UTI

#### **ESRD**

- Up to 50% with PUV will have ESRD in lifetime
  - More modern studies up to about 30% with ESRD
  - Can happen early or later (in twenties)
- UDS evaluation prior to transplant

Tanaka 2011, Sarhan 2011

# Congenital Disorders of the Bladder

- Neurogenic bladder
  - Spina bifida: 29.01/100,000
- Lower urinary tract obstruction
  - Posterior urethral valves: 11.02/100,000
- Prune Belly Syndrome
  - **3.28/100,000**
- Exstrophy-epispadias complex
  - Bladder exstrophy: 1.63/100,000

Lloyd 2013

# **Prune Belly Syndrome**

- The Triad
- Deficiency of abdominal wall musculature
- Bilateral cryptorchidism
- Dilated urinary tract



# Prune Belly Syndrome

- Birth prevalence: 3.8/100,000
- Unknown etiology
- 5% occurs in females: "pseudoprunes"
  - Abdominal wall abnormality
  - Dilated urinary tract
  - Often have omphalocele, lower urinary tract obstruction
  - Up to 40% with anorectoabnormalities

Druschel 1995, Reinberg 1991, Routh 2010

# **Prune Belly Syndrome**

- Smith 2001: morbid condition
  - 20% still born
  - 30% die during initial hospitalization
  - 40% born prematurely
  - 50% significant urinary pathology during lifetime
  - 70% with renal insufficiency
  - 50% with respiratory issues

#### Woodard's Classification

- Category I: most severe
  - Pulmonary hypoplasia and severe renal dysplasia
  - Usually do not survive beyond 1<sup>st</sup> few days of life
- Category II
  - No pulmonary hypoplasia
  - Significant urinary tract involvement with renal dysplasia
  - Typical external features

#### Woodard's Classification

- Category III
  - External features mild or incomplete
  - Uropathy less severe, often with stable renal
  - Stable pulmonary function

# **Genitourinary Manifestations**

- Bladder
  - Thick-walled, enlarged
  - Usually not trabeculated
  - Wide bladder neck
- Prostate
  - Hypoplastic
- Posterior urethra
  - Dilated, elongated
  - Tapers at membranous portion





# **Genitourinary Manifestations**

- Hydronephrosis
  - Often ureteral dilation > hydronephrosis
- Elongated, tortuous, and dilated ureters
  - Distal 1/3 worse than proximal ureter
  - Obstruction <u>not</u> common
  - 85% with VUR



# **Genitourinary Manifestations**

- Testes
  - Usually intra-abdominal
  - Decreased spermatogonia
  - Leydig cell hyperplasia
- Accessory male organs
  - Non union of epididymis
  - Thickened vasa
  - Abnormal seminal vesicles (absent, thick, dilated, etc)

#### **Extragenitourinary Manifestations**

- Abdominal wall muscular deficiency
  - Walking delayed
  - Pulmonary infections and constipation
- Gastrointestinal (30%)
  - Malrotation, volvulus
- Cardiac (10%)
  - PDA, ASD, VSD

- Orthopedic (60%)
  - Hip dislocation
  - Scoliosis
- Limb deformities from oligohydramnios
- Pulmonary (55%)
  - Chronic bronchitis
  - Respiratory insufficiency after URI or anesthesia

## **Evaluation and Management**

- Prenatally: difficult to distinguish from other causes of hydronephrosis such PUVs
- Postnatally: Diagnosis by appearance
  - Creatinine
  - Start prophylaxis
  - Avoid urinary tract instrumentation
  - Orchiopexy b/t 6-12 months
  - +/- urinary tract and abdominal reconstruction

#### Congenital Disorders of the Bladder

- Neurogenic bladder
  - Spina bifida: 29.01/100,000
- Lower urinary tract obstruction
  - Posterior urethral valves: 11.02/100,000
- Prune Belly Syndrome
  - **3.28/100,000**
- Exstrophy-epispadias complex
  - Bladder exstrophy: 1.63/100,000

Lloyd 2013

# Exstrophy-epispadias Complex

- Bladder exstrophy: bladder is an open plate on the low abdominal wall with epispadias
  - **1.63/100,000**
- Epispadias: urethra is a partial or complete open plate on the dorsal aspect of phallus
  - **11.58/100,000**

# Bladder Exstrophy

MALE



**FEMALE** 



# Exstrophy-epispadias Complex

- Cloacal exstrophy: 1/200,000 – 1/400,000
  - Bladder exstrophy
  - Hindgut exstrophy
  - ileocecal junction of bowel is an an open plate
  - ileal intussusception
  - exposed appendices
  - Penis/clitoris split into 2 halves with epispadias



# **Associated Findings**

- Diastasis pubis due to outward rotation of innominate bones
- Umbilical hernias uniform
- Females: absent mons pubis
- Males: short, broad penis
  - Silver 1997: short total corporal length due to foreshortened anterior corporal segment

#### **Common Occurrences**

- VUR almost uniformly after closure of exstrophy due to laterally placed ureters
- Inguinal hernias common
  - Husmann 1990: repair recommended at time of primary repair to prevent incarceration

#### Other Anomalies

- Classic exstrophy and epispadias have a low incidence of other anomalies
- Cloacal exstrophy other anomalies frequent
  - Genitalia: UDT, uterine and vaginal anomalies
  - Skeletal: club foot, hip dislocation
  - neurologic issues: 50-100% have spinal cord involvement

# Diagnosis

- Prenatal findings
  - Absent bladder
  - Lower abdominal protrusion
  - Anterior scrotum with small phallus
  - Low set umbilical cord
  - Abnormal iliac crest widening
- Most often diagnosed at time of delivery

# Newborn Management

- Tie off umbilical cord with suture to avoid trauma to bladder plate
- Plastic wrap on bladder plate, replace daily
- Saline irrigate bladder plate each diaper change

# **Evaluation and Management**

- Baseline RBUS for upper tract evaluation
- KUB to assess level of diastasis
- Spinal ultrasound if sacral abnormality

# **Evaluation and Management**

- Orthopedic consultation to plan for osteotomies if needed
  - >72 hours old, wide diastasis
  - Allows for pubic symphysis apposition, diminishes tension on closure, optimizes anatomic position of the bladder within the pelvis

# **Surgical Repair**

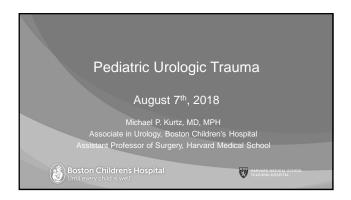
- Staged reconstruction
  - Bladder, posterior urethra and abdominal closure
  - Epispadias repair between 6-12 months of age
  - Delayed bladder neck repair at 4-5 years of age
- Complete primary repair
  - Correct abnormalities in one setting
  - May avoid need for bladder neck reconstruction

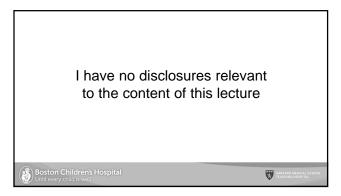
# Congenital Disorders of the Bladder

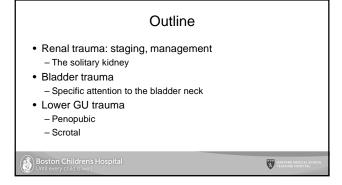
- Overall incidence is low
- Anomalies may be significant with severe consequences
- Early detection and management are critical to prevent further urinary tract deterioration

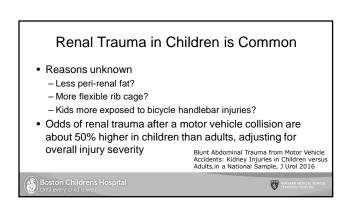
# Congenital Disorders of the Bladder

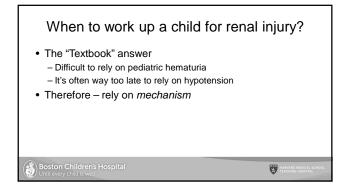
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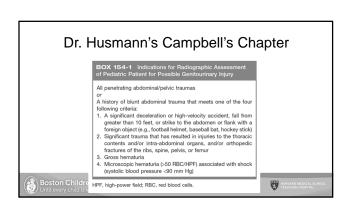












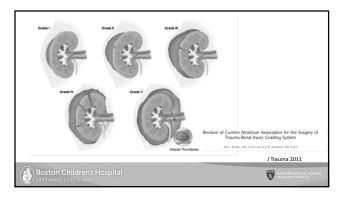
#### A relevant pearl • Blood volume is approximately 70-80 cc/kg (i.e. 7-8% of bodyweight) for children - Even higher percentage in infants and neonates - For adolescents, use adult formula (7%) - Volume is about 0.5% higher in males - Adjust down about 1% (6%) if obese • There are only 5 places you can lose two units of red cells, or equivalent volume in children Boston Children's Hospital

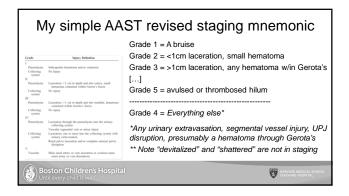
#### What about FAST?

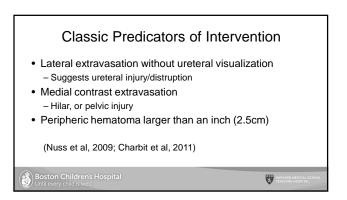
- "Focused Assessment with Sonography in Trauma"
- Initially targeted at hemoperitoneum in unstable patients, and has been expanded to include point-of-care ultrasound in trauma
  - Reardon, acep.org
- Plenty of reports of diagnoses of renal hematoma in children with POC ultrasound
  - Pershad & Gilmore, Ped Emerg Care 2000









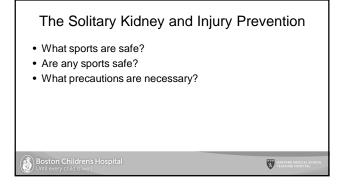


# Post-Injury Follow-up Imaging • For all serious injury (grade 2+) we obtain a blood pressure, UA and ultrasound at 6 weeks – Then DMSA only if question of viability or renovascular HTN – Some reserve imaging only for grade IV and higher or if fragments are devitalized – Concern is for long term renovascular complication • This is distinct from follow-up evaluation for delayed hemorrhage

# Classic Hydronephrosis + Trauma Questions

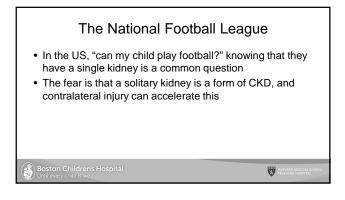
- Preexisting hydronephrosis increases the odds of renal trauma
- Mostly, this is parenchymal rather than a UPJ disruption
- When UPJ disruption is suspected (medial contrast extravasation, no contrast in ureter, minor renal cortical injury), retrograde pyelography can confirm this
- Some authors prefer immediate repair with liberal drain placement; I prefer a nephrostomy and interval repair

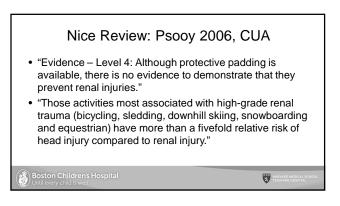


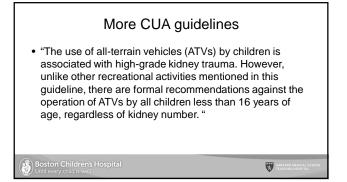


My favorite nephrology line regarding participation in sports with one kidney

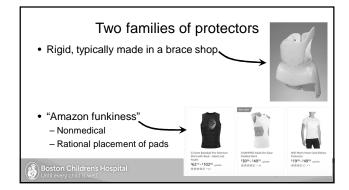
"Well, you only have one head!"

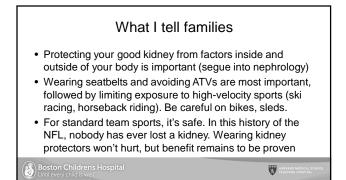


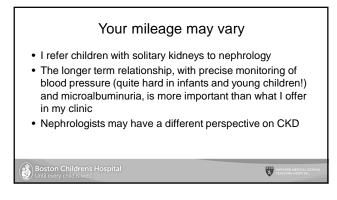


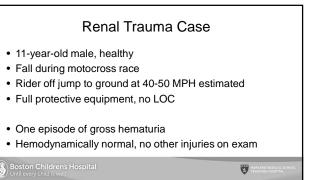


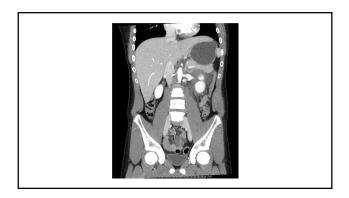










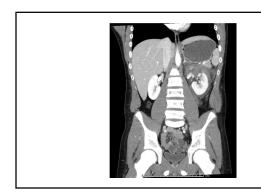




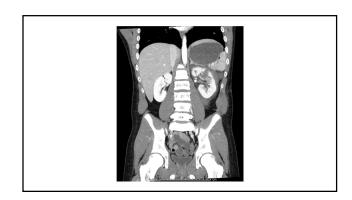






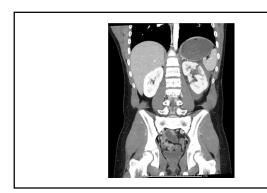






















#### CT obtained before transfer

- 1.8 cm laceration into pelvis, separate >2cm laceration through the lower pole
- No extravasation (portal venous phase)
- No delayed images
- High attenuation hematoma

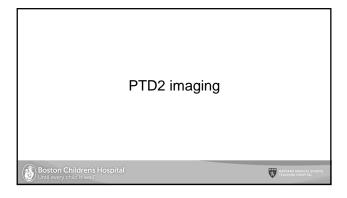


#### Next steps

- Hemodynamically normal
- CT with delays?
- IVP / retrograde?
- Ultrasound?







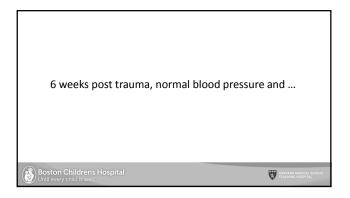






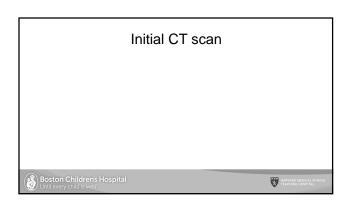


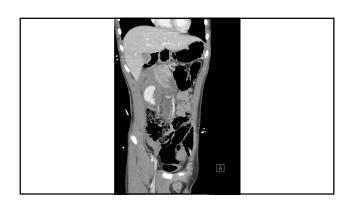




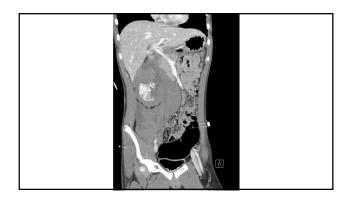


# 2nd Case, Renal Trauma 13yM, previously healthy Belted front-seat passenger, driver veered off road at 50 MPH Rollover, father rescued son from rescued from inverted vehicle, transferred to local hospital and MedFlight to Boston PTD1 Trauma workup reveals pulmonary contusion, no fractures Boston Children's Hospital

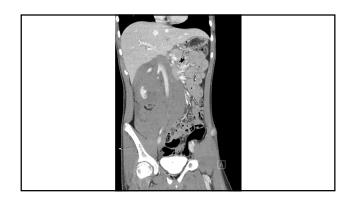


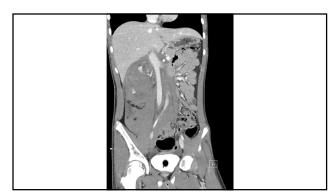






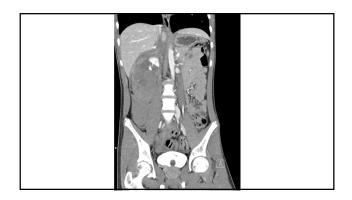








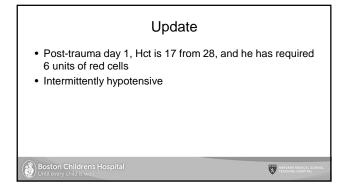


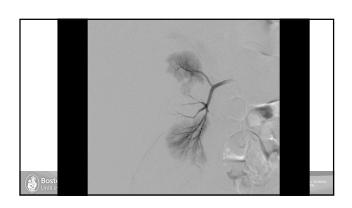




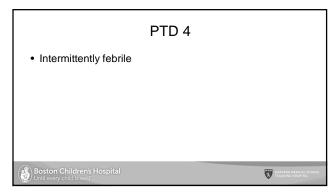








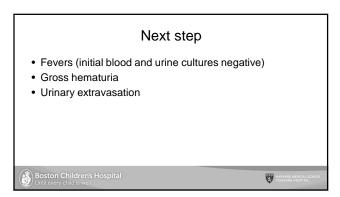




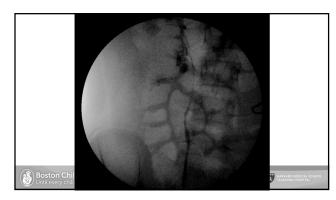




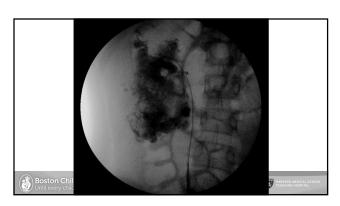


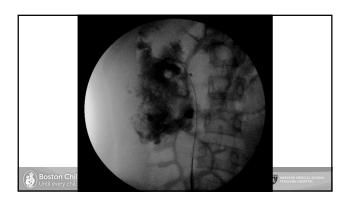


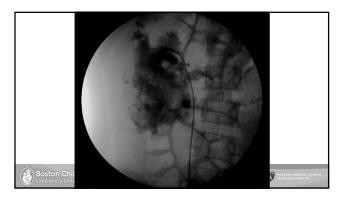


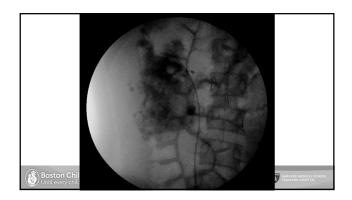


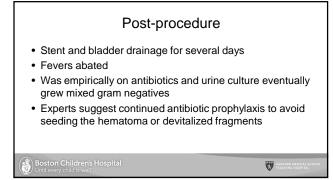


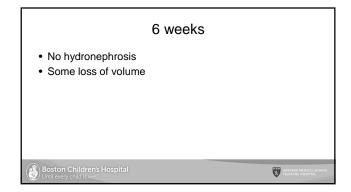


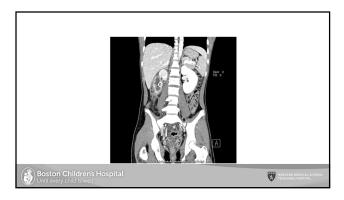






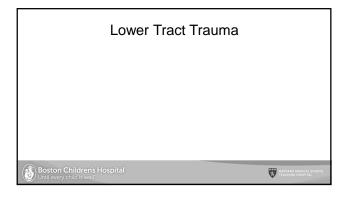




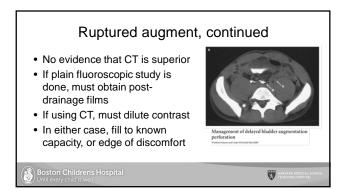


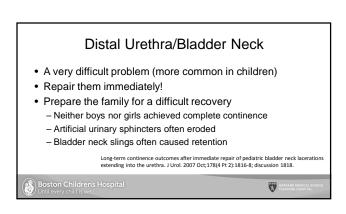


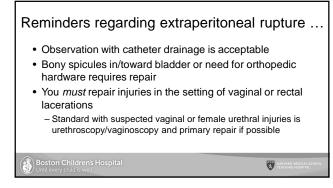


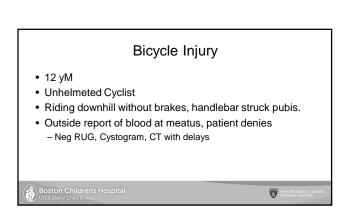


# Ruptured augment A form of trauma – typically a traumatic catheterization not permitting bladder drainage Always an intraperitoneal rupture There are case reports of conservative management I have heard of only one personally, which failed after 8 weeks of drain output! Mortality traditionally is around 3% If they have a peritoneal shunt, we externalize before exploration





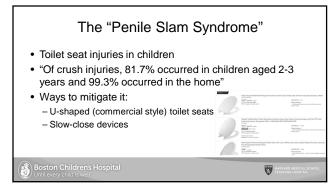


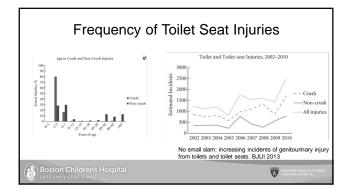




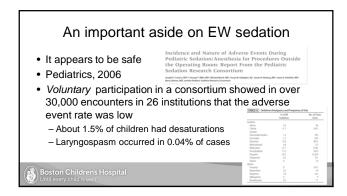


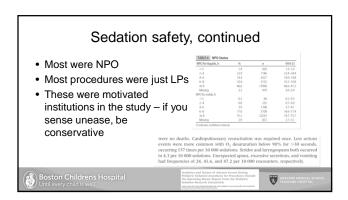


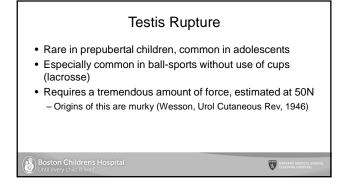


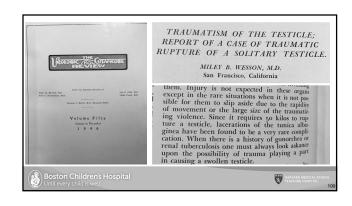


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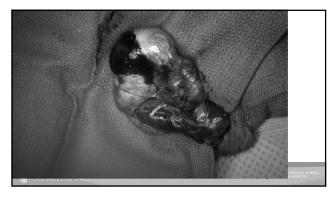




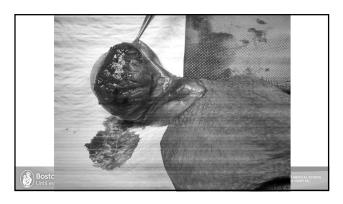




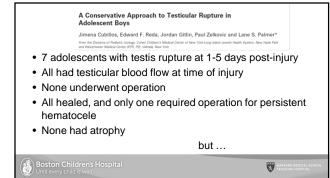


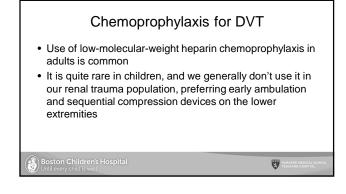


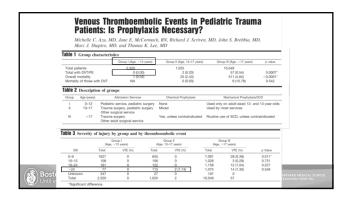


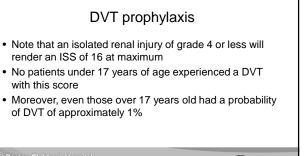


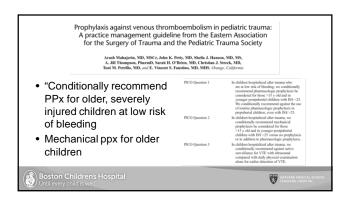


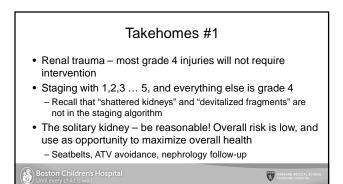


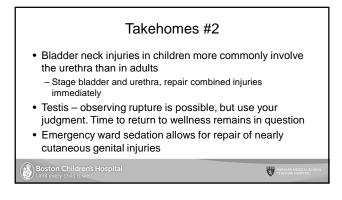




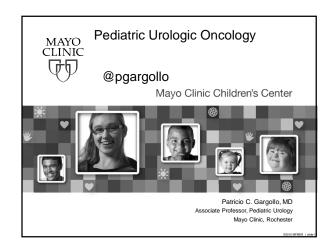


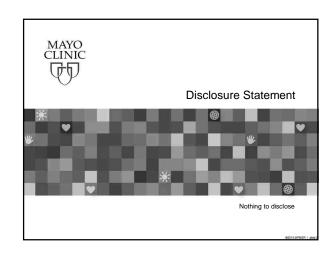




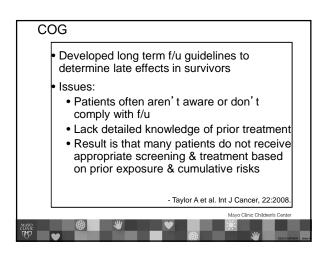


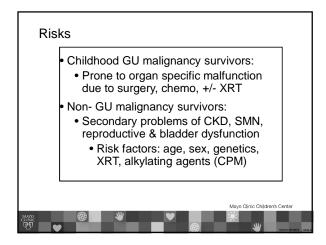


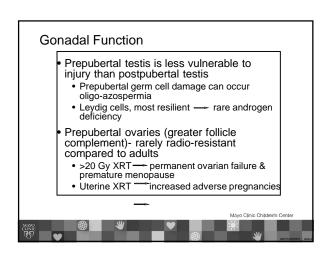


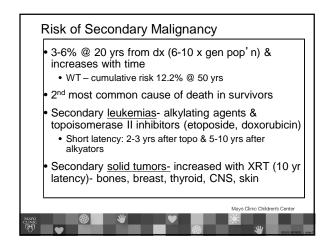


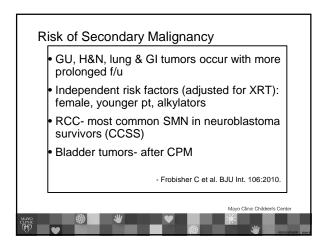
# Pediatric Oncology Overall childhood cancer survival rate >70% Price of survival= more "intensive" protocols= long term adverse sequelae 1:450 young adults in USA is childhood cancer survivor CCSS: > 73.4% will have a chronic health problem prior to age 40 & 1/3 of them are life threatening 18.1% cumulative mortality rate @ 30 yrs from dx Oeffinger KC et al. NEJM 355:2006.

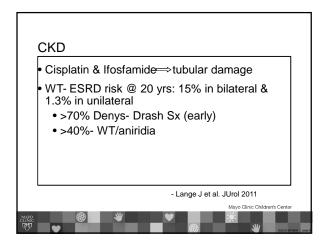


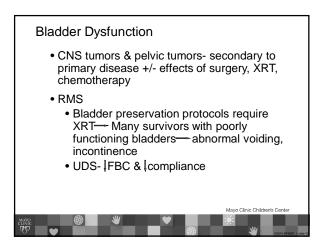


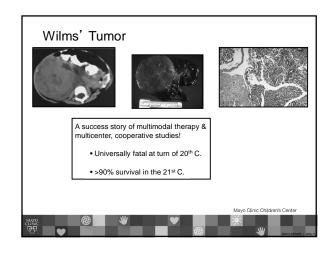


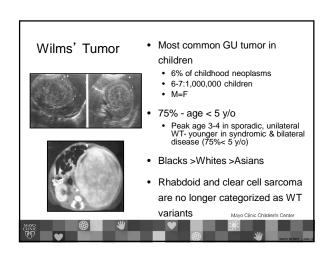


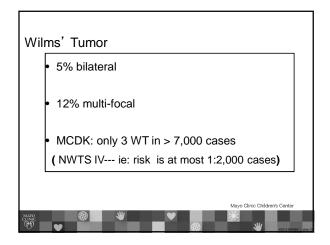


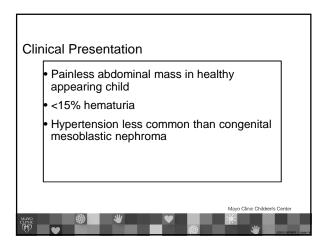


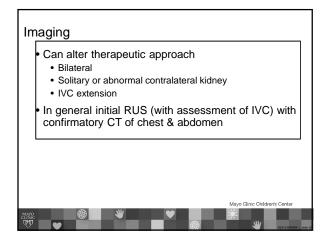


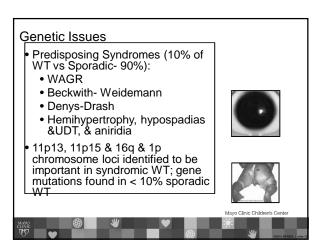


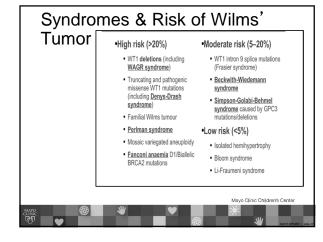


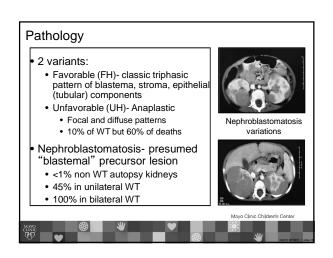


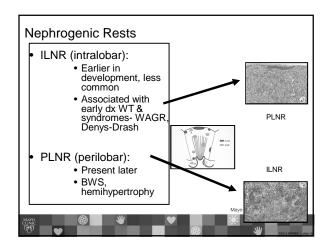


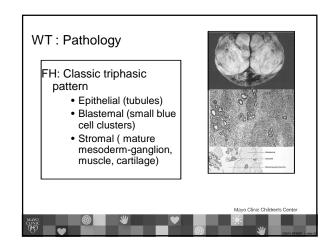


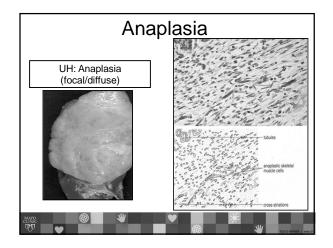


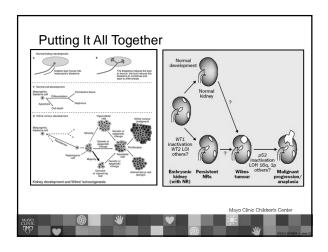


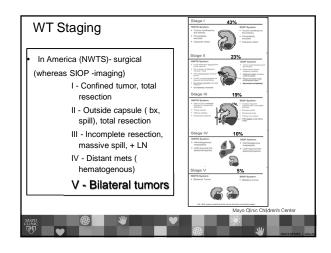


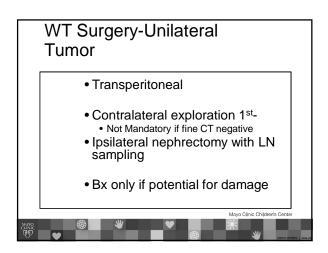


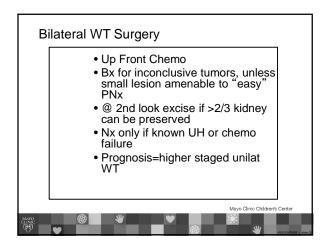


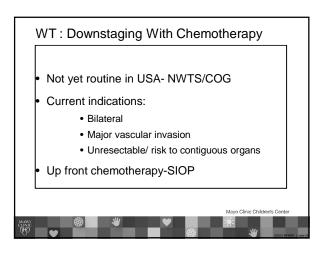


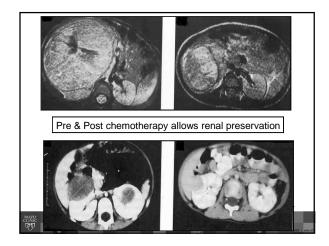


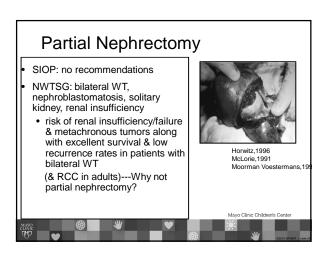


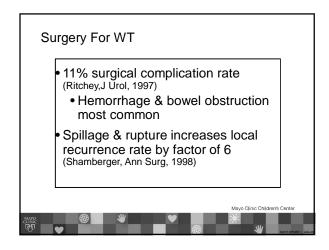


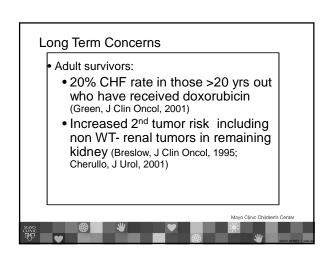




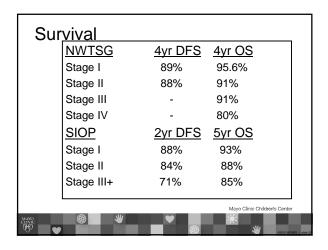


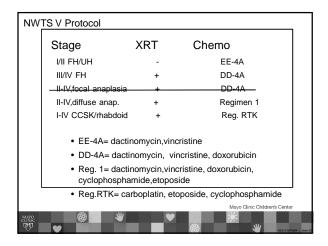


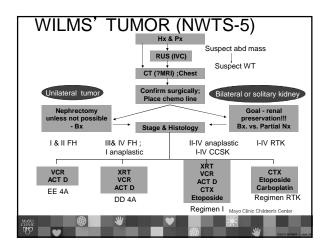


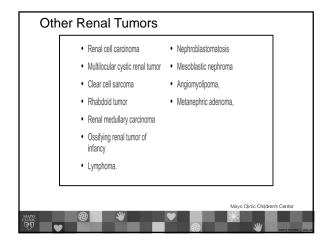


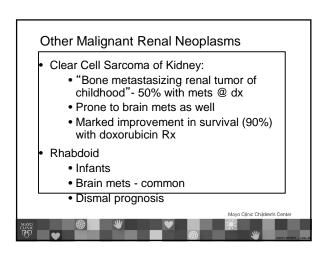
Stage	Histology	Survival(%)
I	FH	97
II	FH	92
Ш	FH	84
IV	FH	83
I-III	UH	68
IV	UH	55
All	FH	89
CCSK	-	75
Rhabdoid	-	26 Mayo Clinic Children's Cent

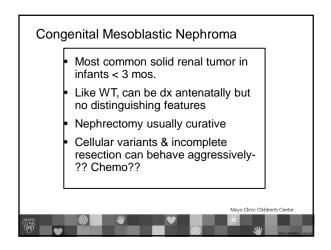


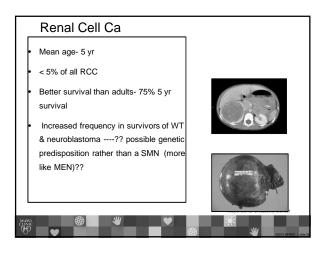


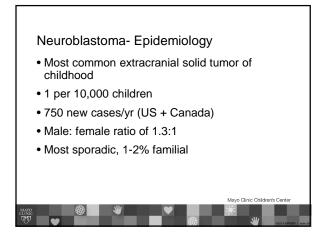


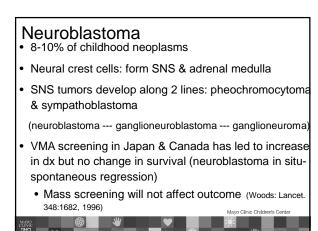


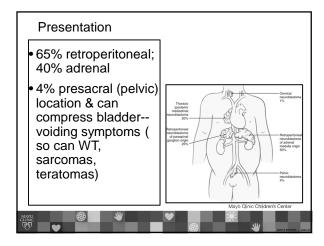


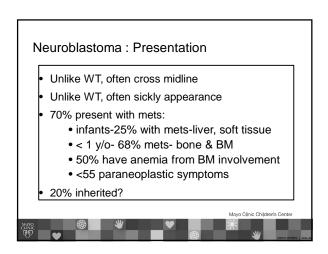


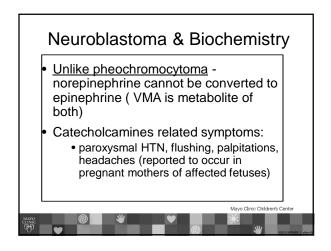


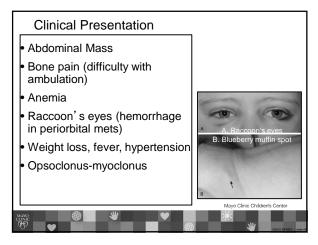


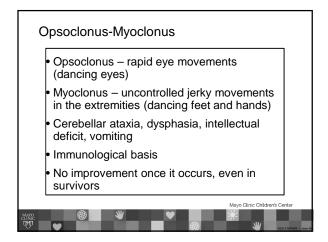


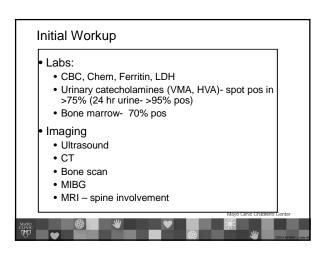




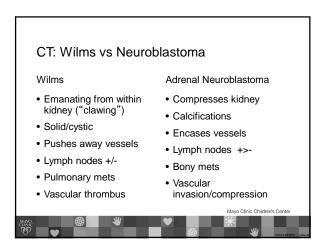


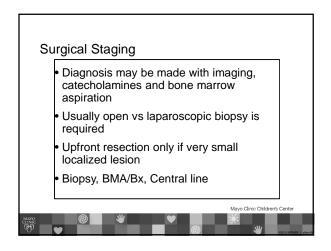


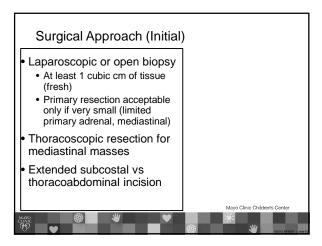


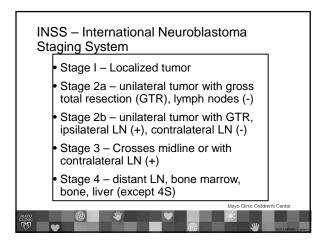


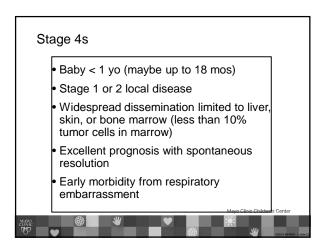


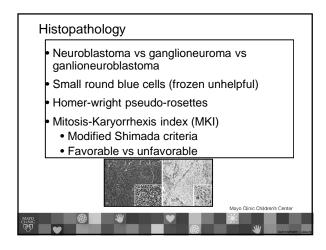


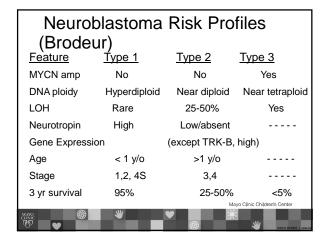




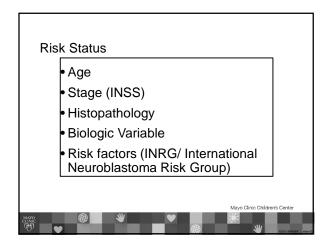


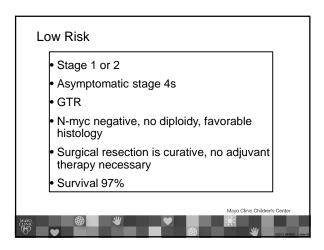


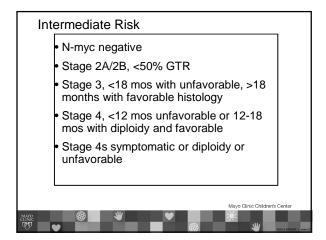


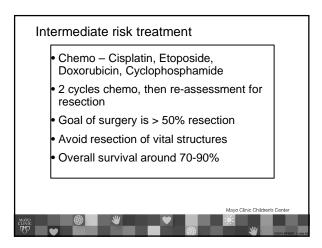


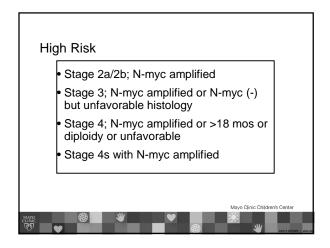
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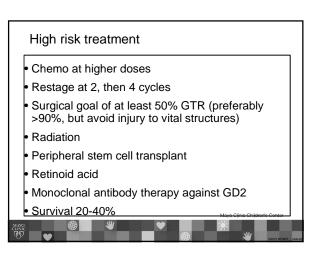


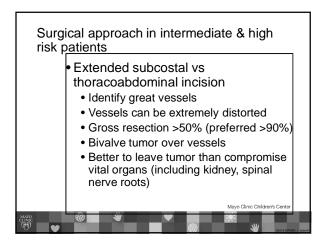


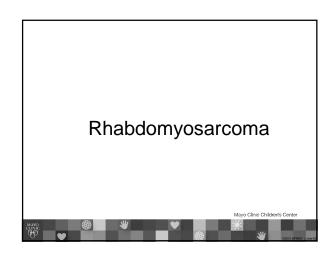


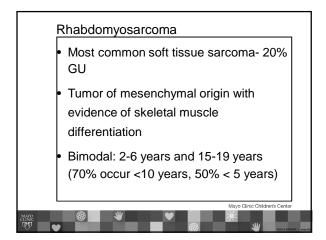


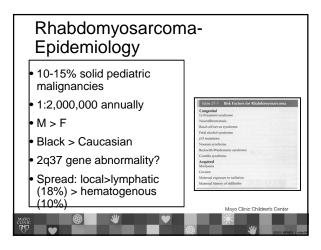


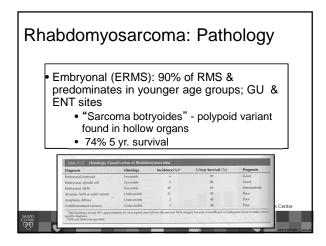


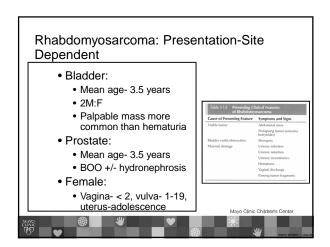


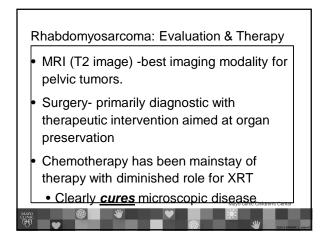


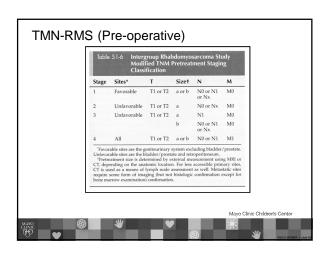


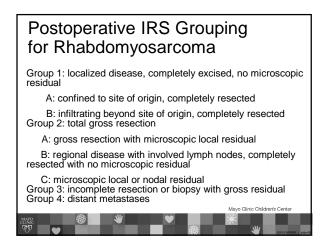


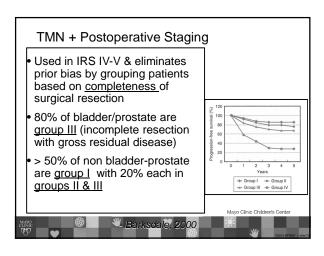


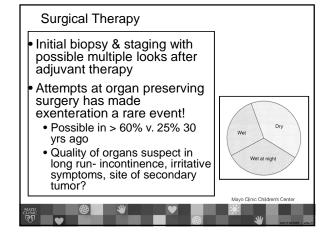


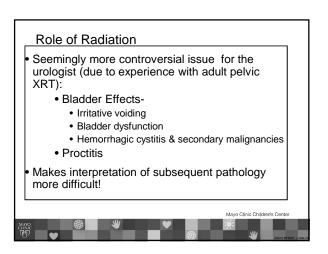


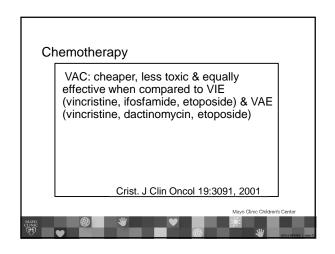


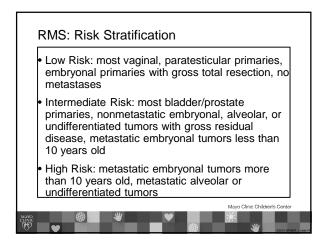


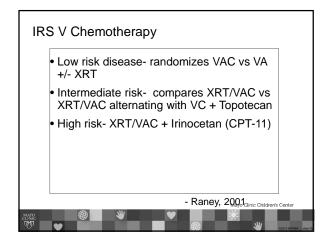


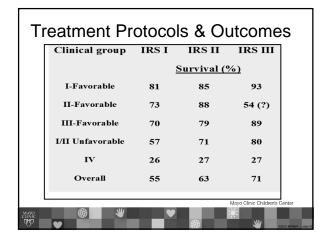


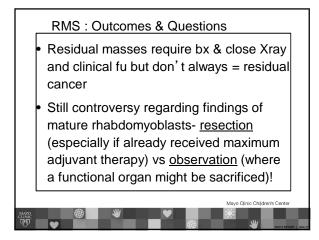


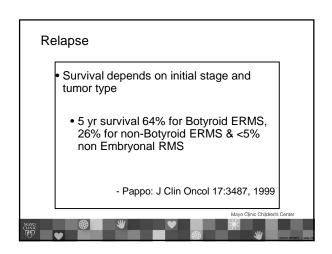


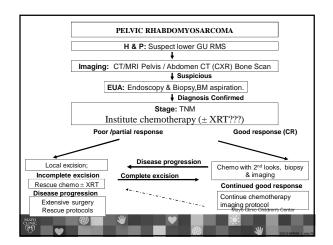


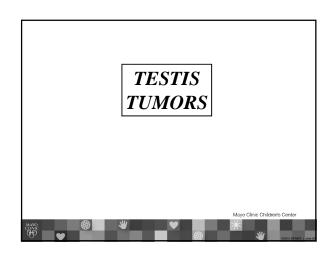


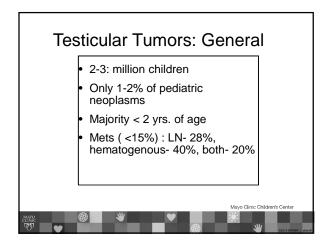


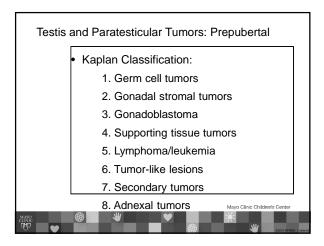


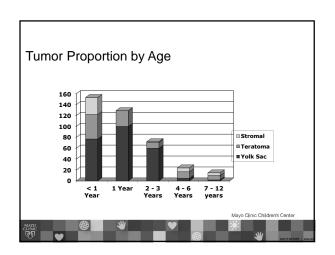


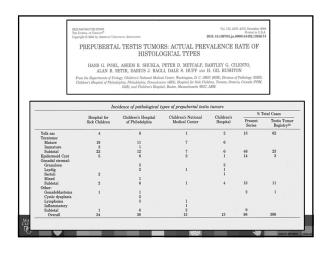




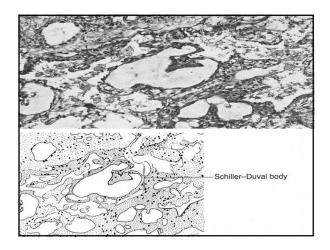


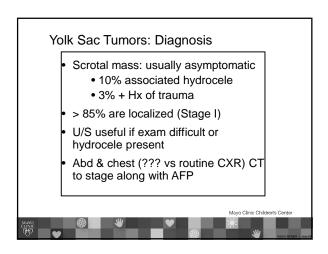


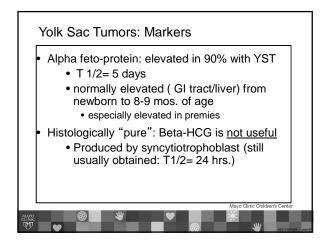


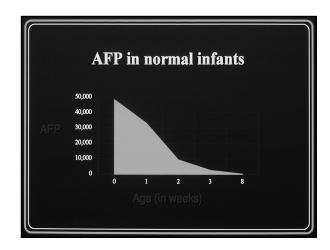


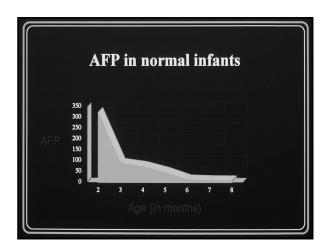
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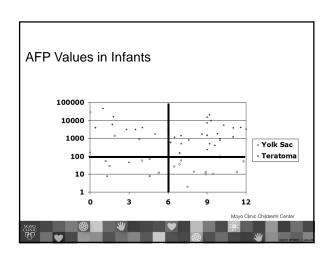


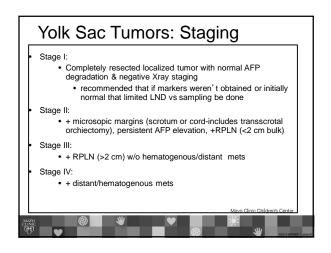


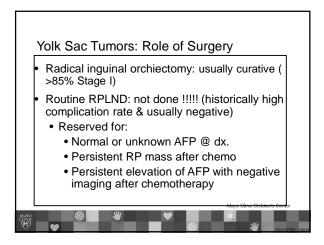


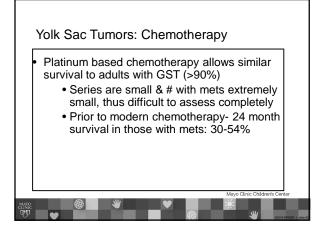


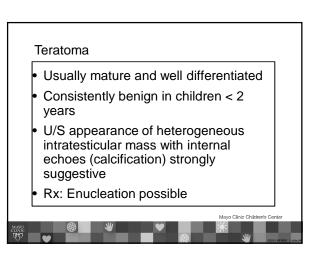


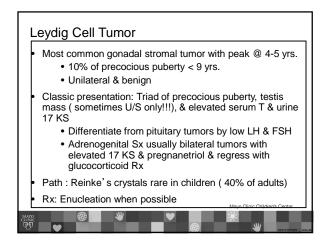


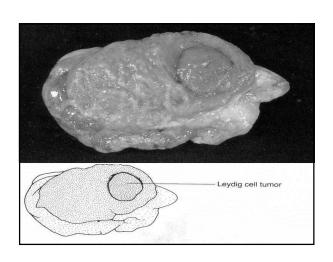


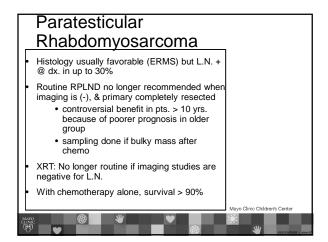


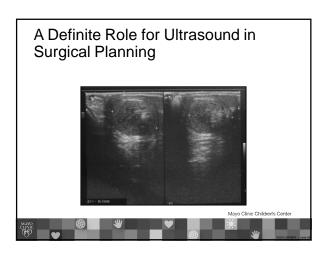


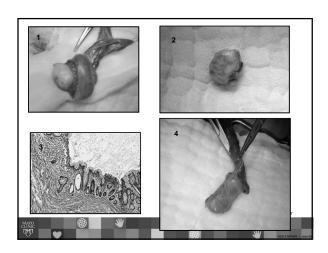


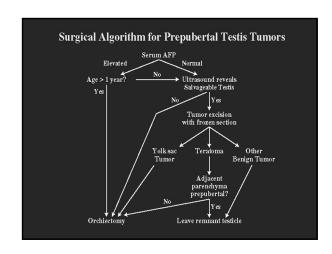




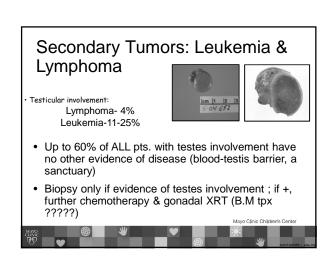


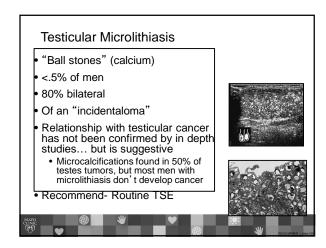


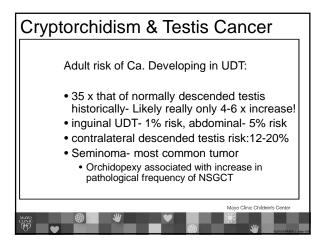


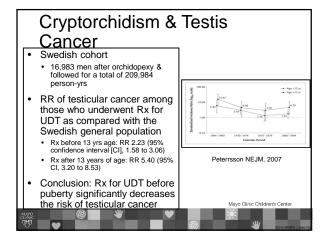


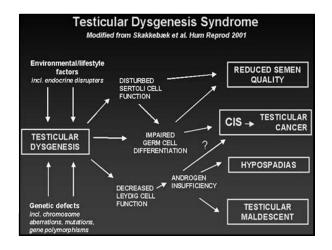
# Gonadoblastoma Develop in patients with an abnormal gonad whose karyotype contains a Y chromosome.(Intersex conditionsgonadal dysgenesis, testicular feminization) 80% phenotypic females with 46 XY 22% streak, 18% dysgenetic, 60% indeterminate Bilateral in 10-33% Benign tumors - as germ cell elements outgrow stroma, 10-60% will progress to malignant dysgerminoma (seminoma), after puberty!!!!! Rx: Gonadectomy(ies) in @ risk patients-early





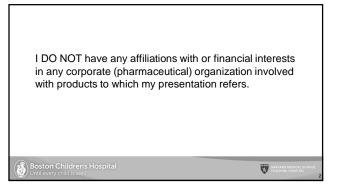


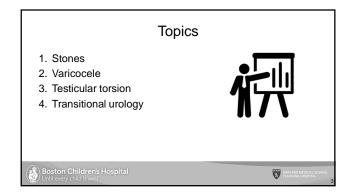




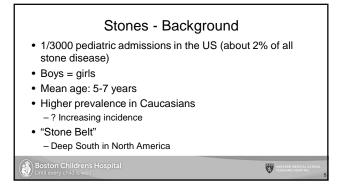


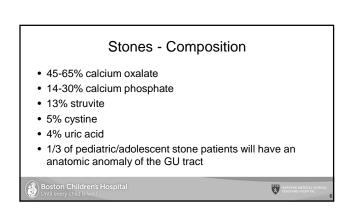


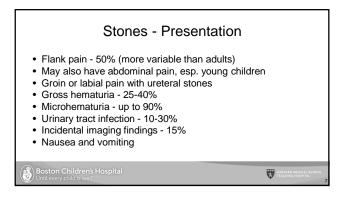


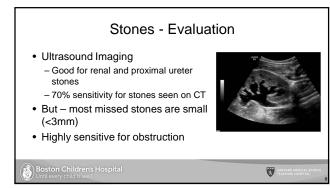




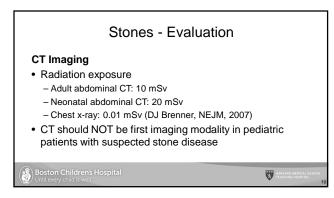


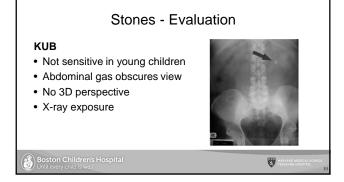


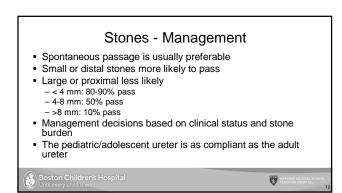


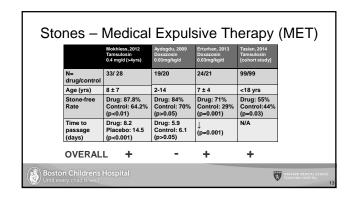








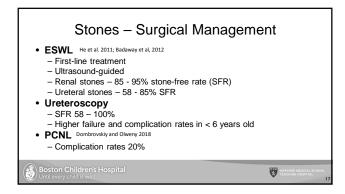


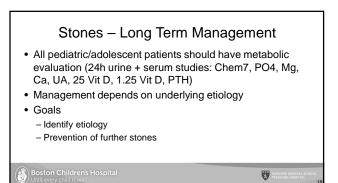




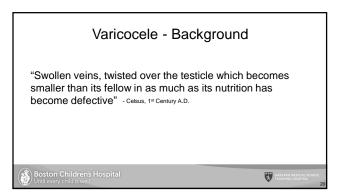
# Stones – Medical Management Close follow-up is essential 1-2 weeks Strain all urine when possible Immediate re-evaluation if febrile If no stone passage within 2 weeks – proceed to surgical treatment High-grade obstruction persisting longer than 6 weeks may lead to irreversible renal injury

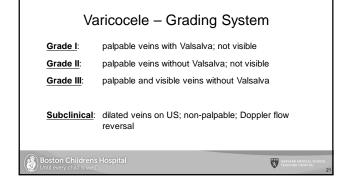


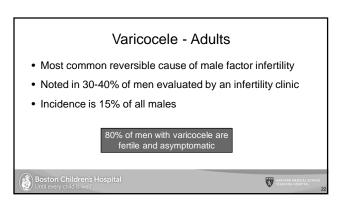


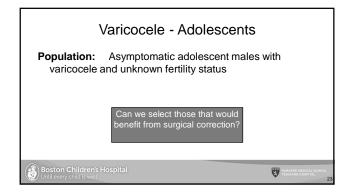


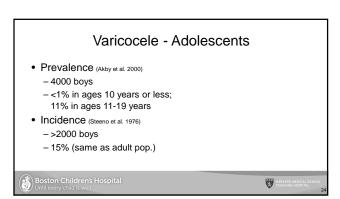


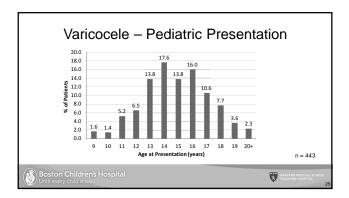


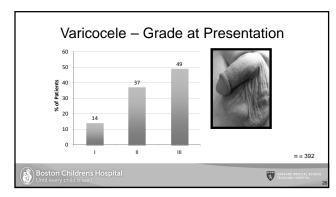


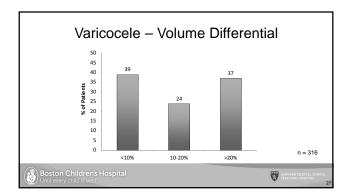


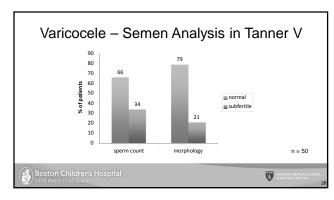


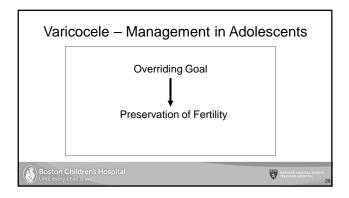


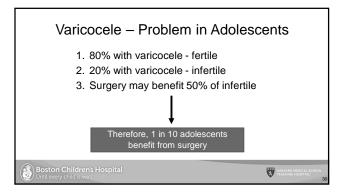


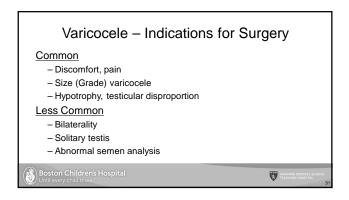


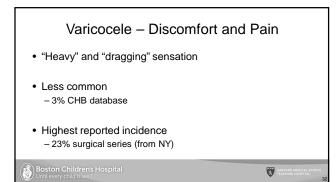


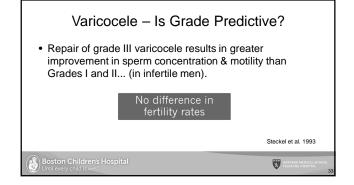


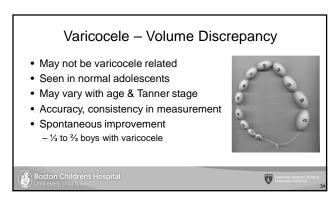


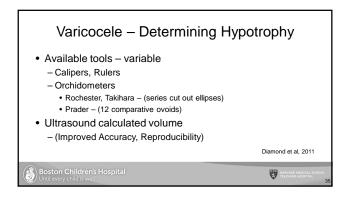


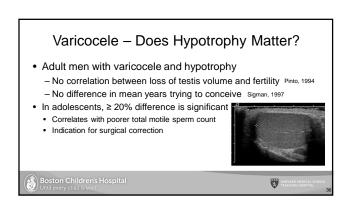


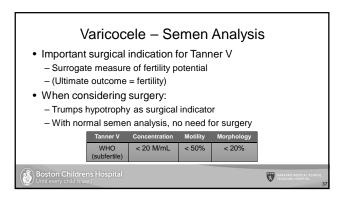


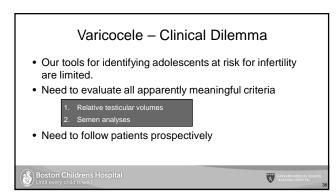




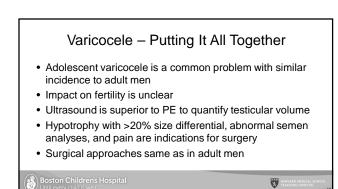


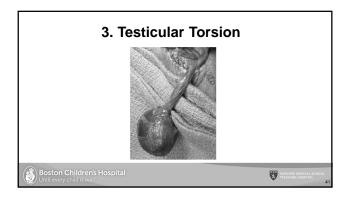


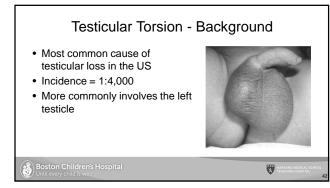


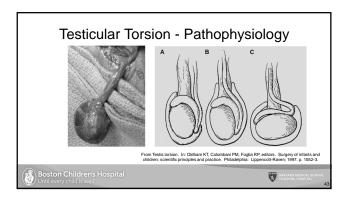


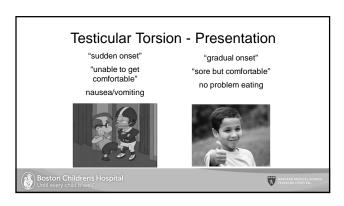


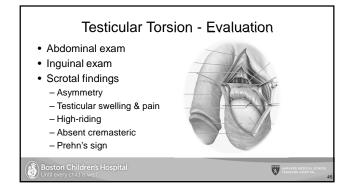


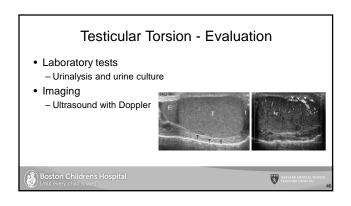


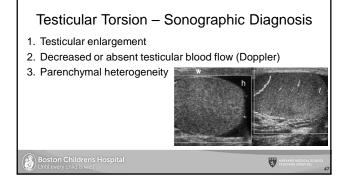




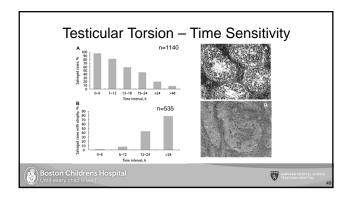


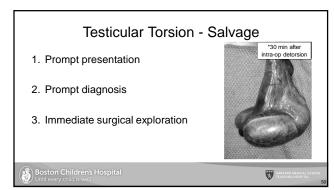




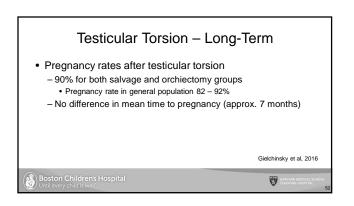




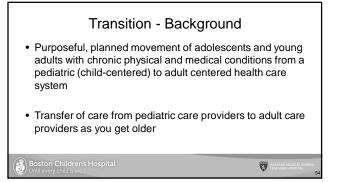












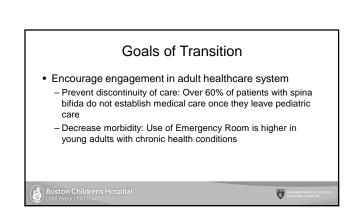
### Transition - Background

- Taking care of adults is different than taking care of children
- Patients with spina bifida have increased medical needs than the general population and they need specialty care as adults



### Brief History of Transition in the US • 1984- "Youth with Disability, The Transition Years" • 1989- Surgeon General "Growing up and Getting Medical Care: Youth with Special Health Care Needs" • 1990- Maternal and Child Health Bureau "Youth with Disabilities: A National Response" • 2002- AAP, AAFP & ACP Consensus Statement - 1) understand the rationale for transition - 2) have the knowledge and skills to facilitate that process - 3) know if, how, and when transfer of care is indicated

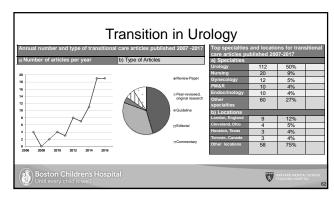
### Brief History of Transition in the US • 2007-AAP Annual Leadership Forum "top-10 priority" • 2011-AAP recognized that widespread implementation had not been recognized — Pediatric providers were unclear on goals of transition — Limited availability of adult providers • 2013- "Current status of transition preparation among youth with special needs in the United States." — Less than 40% of individuals met transition core outcome measures • 2014- Got Transition ™ (gottransition.org) and AAP Pediatric ECHO

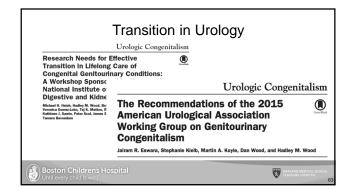


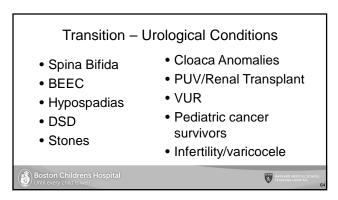




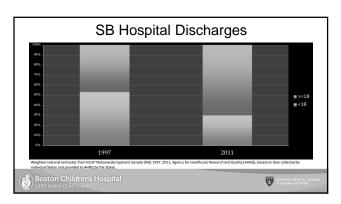


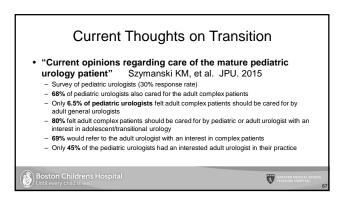


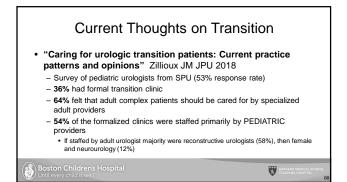




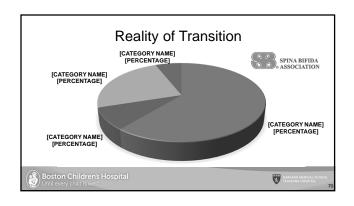












# Current Models of Transition • Effective transition policy • Implement transition tracking (registry) • Assessment of transition readiness • Transition planning • Transfer to adult care/Adult approach • Completion transfer/Ongoing care

